SECOND SERIES SEPTEMBER 1943 VOL. 19, NO. 9

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

SEPTEMBER, 1943

MALARIA AND ITS INFLUENCE ON WORLD HEALTH

*The Hermann M. Biggs Memorial Lecture**

PAUL F. RUSSELL

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INTRODUCTION

"FROM the standpoint of prevalence, malaria appears to be the most important of all diseases in the world today." This statement is based on wide experience and great authority, for it is the first sentence in that excellent treatise on tropical diseases by Admiral Stitt and Colonel Strong.[1] Adequate morbidity and mortality statistics regarding malaria do not exist, yet it is generally believed by those who have studied the subject, that no disease has, or has had through centuries, a more profound influence on world health than malaria. Medically oriented historians suggest that this disease has postponed development of the tropics for centuries, and that it has accelerated the decline of nations. Even today this preventable mosquito-borne infection is the greatest enemy of merchant, soldier, administrator, and farmer in all of the warmer countries.

* Given April 1, 1943 at the Stated Meeting of The New York Academy of Medicine.

Such sweeping assertions seem rash in the United States where in 1941 the mortality rate for malaria in fourteen Southern states was only 2.73 per 100,000.[2] Taking the census registration area of the whole country, the death rate from malaria in 1900 was 7.9 per 100,000 but only 1.1 in 1940.[3] Relatively few can recall local conditions of six or seven decades ago when our South was highly malarious and even such northern states as Michigan, Illinois, Indiana, and Ohio were afflicted. For instance, the death rate from malaria in Michigan in 1880 was 19.5 per 100,000. As late as 1900, Memphis had a malaria mortality rate of 200 per 100,000, and Savannah almost as great.[4] High as these urban malaria rates appear, they were about a fifth of those obtaining in such tropical cities as Singapore as late as 1911.[5]

Malaria at present extends as far north as 60° N. latitude (in Russia) and as far south as 40° S. latitude (in Argentina). It is found as low as the Dead Sea (1,300 feet below sea level) and as high as Quito in Ecuador (9,000 feet). But malaria is a focal disease and is not evenly distributed nor uniformly prevalent in any country. In the United States it is most common in the southeast, although it extends as far north as Illinois and Indiana, and also occurs in California.

There is a great deal of hyperendemic malaria between 45° N. and 40° S. latitude, in the plains and foothills of Central America, north and northeast South America, Central Africa from the Atlantic to the Indian Ocean, North Africa, south and especially southeast Europe, Turkey, the Levant, Iraq and Iran, Afghanistan, India, Ceylon, Burma, South China, Indo-China, Siam, Malaya, Netherlands Indies, Formosa, the Philippines, and many islands of the Pacific which are west of 170° E. longitude and north of 20° S. latitude. (The Fiji Islands and Samoa, for example, are not malarious but the New Hebrides suffer severely.)

Malaria is hyperendemic in many areas of the littoral of some of the world's great seas and gulfs, the names of which connote vistas of sand and coral, mangrove and coconut, with a wide variety of peoples and topography, encircling the globe. The Caribbean, Mediterranean, Tyrrhenian, Ionian, Adriatic, Aegean, Black, Azov, Caspian, Red, Arabian, East and South China, Sulu, Celebes, Java, Banda, Timor, Arafura, and Coral seas, the Bay of Bengal, the gulfs of California, Mexico, Honduras, Panama, Guinea, Persia, Oman, Siam, and Tonkin, all are bordered, in part at least, by highly malarious regions.

To many of the countries within the hyperendemic malaria zones this disease, which has been a medical curiosity in much of our own country, is bringing not only physical disaster but economic and social tragedy. In India, for example, malaria is a veritable juggernaut disease. There it kills at least a million persons every normal year, more in epidemic times. Another million die from indirect results of malaria. Throughout all Hindustan there are each year at least 100,000,000 cases of malarial fevers. Quoting Sinton:[6] "There is no aspect of life in that country which is not affected, either directly or indirectly, by this disease. It constitutes one of the most important causes of economic misfortune, engendering poverty, diminishing the quantity and the quality of the food supply, lowering the physical and intellectual standard of the nation, and hampering increased prosperity and economic progress in every way."

Hehir,[7] a competent observer, wrote: "It may with confidence be said that the eradication of malaria in India would in a single generation convert that country into one of the most prosperous in the world." It is now one of the least prosperous so far as the vast majority are concerned. Average incomes in rural South India are as low as a dollar a month.[8]

What the actual sum total of malaria is today, no one knows, or can estimate closely. But one would venture to assume from such data as are available and from personal acquaintance with certain areas, that there are not less than 3,000,000 malaria deaths and at least 300,000,000 cases of malarial fevers each year, throughout the world.

These facts are of greater concern to us now than ever before. In this global war our armed forces are operating in some of the world's most malarious areas. We have already felt the impact of this debilitating fever in such places as Panama, West Africa, Burma, New Guinea, and the Solomon Islands. In such areas malaria is by all odds the greatest disease hazard to our soldiers; indeed, in some places it is a greater menace than the enemy. To more than one of our medical officers malaria is no longer an exotic disease but a difficult military problem.

Earliest Days

The history of malaria extends so far back into antiquity that speculations as to when and where it first appeared are futile. Certainly the

present great library of malariology represents cumulative endeavors of many generations of priests and philosophers, parasitologists and physicians.

In early days, when natural causes of all disease were hidden, it was inevitable that man should attribute malaria to black magic of wizards, evil eyes of enemies, offended spirits of dead men, animals, or plants, maleficent mediation of gods and goddesses of wood and stone. Malaria prophylaxis was then, as it is in Central Africa and the Solomon Islands today, a practice of white magic, charms and spells, fetishes and taboos, plant lore, and sacerdotal hygiene, a hocus-pocus conjured up to exorcise, conciliate, or propitiate superhuman beings and powers.

Gradually man came to prefer natural to supernatural explanations. Still looking through a glass darkly, he spoke of malaria epidemics as dependent on alterations in astral currents or lunar rays, or generated by terrestrial perturbations and tremors. He discoursed learnedly of febrific effluvia, vegeto-animal exhalations, and mephitic airs.

Ancient Greece and Rome

The ancient Greeks 2,000 years ago recognized quartan, tertian, quotidian and semitertian (probably malignant tertian) varieties of malaria. They also were aware that the disease had seasonal and topographical features. In particular, they associated the intermittent fevers with marshes and marsh vapors. Hippocrates in the fifth century B.C., wrote of the enlarged spleen of inhabitants of marshy regions.

Then there was a Greek story (perhaps apocryphal) of Empedocles of Agrigentum who controlled an epidemic in Selinus, Sicily, about 550 B.C., partly by draining the marshes and partly by turning two rivers into them so that, as Matthew Arnold wrote, Empedocles was able to "cleanse to sweet airs the breath of poisonous streams." Whether or not Empedocles was dealing with malaria, certainly there are many passages in the Greek which clearly connect this fever with marshes.[9]

Roman writers, also, were acquainted with paludism and were suspicious of swamps. For instance, the Republican agriculturalist, Varro (116-28 B.C.), in his *Rerum Rusticarum* wrote that in marshes "certain minute animals are bred, invisible to the eye and, borne by the air, reach the inside of the body by way of the mouth and nose, and cause diseases which are difficult to be rid of."[10]

Fabius Maximus and Julius Caesar suffered from intermittent fever

and during the Civil Wars the health of Caesar's army was shattered by it.[10] Cicero wrote of the "*old* Fever Temple on the Palatine," indicating that the cult of the Fever Goddess in Rome was very ancient.

Then, too, there was a famous passage from Columella (about the first century B.C.) which stated that "marshes threw up noxious steams and bred insects, armed with mischievous stings, and pestilent swimming and creeping things whereby hidden diseases were often contracted, the causes of which even the physicians themselves could not thoroughly understand."[10]

Thus, in ancient Italy, as in ancient Greece, both medical and lay authors recognized the intermittent fevers and clearly surmised an etiological relationship between these fevers and low marshy places. This is easy to understand because the malarial fevers, with their characteristic periodicity, even to this day in Greece and in Italy are often most prevalent near marshes. There was a good deal of malaria in ancient Greece, where it was apparently introduced during the fifth century B.C. In fact, Ross,[9] Jones,[11] and others have suggested that malaria was a contributing factor in the great decline in moral and intellectual vigor which took place in Greece between 500 and 300 B.C. It has also been postulated that malaria had a similar disintegrating effect in ancient southern Italy.[11] Some historians, as Childs,[12] believe that while disease is mighty over the individual, parasites and viruses have played an unimportant role in social history.

However that may be, by the latter part of the Middle Ages, the "Roman Airs" had a bad name throughout all Christendom. For instance, Celli[10] records that Peter Damian in the eleventh century tried to give up the episcopal see of Ostia, forced on him by Pope Stephen IX. He wrote the following verses:

"Rome, voracious of men, breaks down the strongest human nature,
Rome, hotbed of fevers, is an ample giver of the fruits of death."

In the twelfth century, Roman fevers are said to have destroyed the army of Frederick Barbarossa, and this was commemorated in verse by Godfrey of Viterbo, who wrote

"Those from whom Rome was unable to defend herself,
were dispersed by the air
at whose breath the German youth fell."

The great Arab physicians of the eighth to thirteenth centuries wrote of these intermittent fevers but, in general, active interest and

speculations on etiology subsided with Galen in 200 A.D., not to be aroused again until the seventeenth century.

Seventeenth and Eighteenth Centuries

In the seventeenth and eighteenth centuries there were great advances in knowledge of therapy and of etiology of intermittent fevers.

THERAPY

In the seventeenth century European physicians learned that the bark of a South American tree is an effective remedy for the intermittent fevers. There have been many accounts as to how this came about. Apparently the bark was first known in Peru, where the first recognized use of this bark was in 1630,[13] but whether natives had recognized its medicinal qualities before Pizarro invaded their country in 1512-1533 is unknown. The traditional anecdote, dating back many years, appears to have little historical basis. It told of the fever of Ana de Osorio, the first, or of Francisca Henriquez de Ribera, the second wife of the fourth Count of Chinchon, Viceroy of Peru. A friend, as the story goes, sent to the Count's physician a parcel of powdered bark of the quina-quina tree, a substance that had once cured him of "tertiana." The physician, Don Juan de Vega, having tested the powder on a number of patients, is reported to have administered it to the Countess with great success. About 1640, the enthusiastic Vicereine, or her physician, or some Jesuit father, is said to have sent or carried samples to Europe.

This story has suffered a serious blow in the recent discovery of the official diary of the Count of Chinchon,[14] wherein is a careful day-by-day account of the Chinchon family. It now appears that the first countess was blessed with amazing good health. Aside from a sore throat and a "flux and cough on the lungs" she had no illness at all in Peru. The noble count himself was frequently ill with malaria, but nowhere is it recorded that he experienced a dramatic cure by fever bark. The countess did not take bark back to Europe, for she died in Colombia, on the way home, of what seems to have been yellow fever.

The true, albeit less romantic, account of the advent of cinchona bark in Europe appears to be that of Haggis,[15] who made a scholarly search among original documents. He notes that during the last decades of the sixteenth and throughout the seventeenth century there was a

brisk trade in medicinal barks and herbs from South America to Spain and Italy. One item in considerable demand was a bark, which because of its medicinal properties was called quinua-quinua by Peruvians and which is now known to have been from the tree *Myroxylon peruiferum.* In commerce this bark was referred to sometimes as Peruvian and at other times as quina-quina bark. Peruvian balsam was extracted from it and was used as a non-specific febrifuge. When demand came to exceed supply, the exporters began to substitute another bark of similar appearance, which from the evidence must have been taken from cinchona trees. For some decades during the seventeenth century the dual source of so-called Peruvian bark led to confusion among physicians as to its real value in treating the intermittent fevers. But gradually the adulterant replaced the original bark completely. Thus, as has been pointed out,[14] it would appear that we owe the discovery of one of our most useful chemotherapeutic remedies to dishonest traders rather than to keen-eyed scientists.

The earliest mention in European literature of the use of cinchona was by Heyden in 1643, so the remedy must have been introduced before that. Powdered bark had been sent from Spain and Italy to England by 1655 and was used in this form against the intermittents for about two centuries. The bark was known in the North American colonies. For instance, in 1776 the Continental Congress ordered the medical committee to forward 300 pounds of bark to the southern department for use of the troops. Jackson, a British Army surgeon in the forces of Lord Cornwallis, used the bark extensively to treat intermittent fevers among British troops in their southern campaigns.[16]

The first man to describe the fever tree scientifically was Charles Marie de la Condamine, an astronomer, who in 1735 led an expedition from France to measure an arc of the meridian near Quito, Ecuador, in order to determine the shape of the earth. He quarreled with his associates and quit them to explore the Amazon, and eventually the Peruvian country. But it was the Swedish botanist, Carl von Linne, the great Linnaeus, who gave the name *Cinchona* to the quina-quina tree. His misspelling of the name of the Countess has been perpetuated.

Two French pharmacists, Pelletier and Caventou, isolated the alkaloids *quinine* and *cinchonine* from cinchona bark in 1820. Since then many other alkaloids have been isolated from this Peruvian bark but only four occur in any considerable amounts. These are quinine and

quinidine, cinchonine and cinchonidine, all of which exert a therapeutic action on malaria.

Demand for cinchona bark increased rapidly, and the trees, which grew wild, were recklessly destroyed. It occurred to several scientists that the tree could probably be grown in other tropics as well as South American. In 1743, de la Condamine attempted to take cinchona plants to Europe but they were all swept off his ship by a wave in the river Amazon before he had even left South America. In 1849, cinchona trees were planted unsuccessfully in Algeria. The Dutch, in 1852, sent Justus Charles Hasskarl, a courageous botanist, on a hazardous collecting expedition which took him across the Andes into Bolivia and Peru. He was successful, by a narrow margin, and began cinchona cultivation in Java in 1854. His Government rewarded him with a knighthood of the Netherlands Lion and a Commandership of the Oaken Crown.

In 1860, the British sent out a party under the exceptionally able leadership of Clements R. Markham, a geographer and archaeologist. As a result of his work a cinchona plantation was started in the Nilgiris Hills of Madras Presidency near Ootacamund, where over two and a half million trees were growing by 1872. This plantation is still a source of government quinine for use in India. Markham was knighted for his achievements.

The seeds and seedlings of these early Dutch and British expeditions were not the best yielding varieties of the fifty or more species of cinchona trees growing in South America. The most successful collector of high quality seeds was an Englishman named Charles Ledger who had been living in the cinchona belt and knew the difference between strong bark and feeble. He sent his West Indian servant Manuel for seeds of a tree which he knew had a high quinine content in its bark and which he had seen growing in a certain place. The good Manuel was gone five years, because four April frosts destroyed the flowers and prevented ripening of fruit of the particular trees which met his requirements. But, finally, he came back with the seeds. Sent out again he was seized by Bolivian officials, jealous of their bark monopoly, and, although imprisoned, severely beaten, half-starved, and robbed of all his possessions, he refused to tell for whom he was collecting seeds and was at last set at liberty, to die soon afterwards of his ill-treatment.

Ledger, in 1865, sent fourteen pounds of high quality seeds to his

brother George, who lived in London. George Ledger attempted to sell them to the British Government who were not interested. However, he finally sold half of the seeds to the Dutch for a few guilders and the other half to a Madras planter. Within eighteen months of this sale the Dutch had 12,000 plants ready to set out and five years later their analyses of bark were showing from 8 to 13 per cent of quinine, whereas no other bark on the market could show much over 4 per cent. The seeds sent to Madras also in time grew well but on a much more limited scale; this species was officially named *Cinchona ledgeriana.* The Dutch did a good deal of experimenting with hybrids and successfully developed the world's best cinchona trees. At the outbreak of this war, Java had some 37,500 acres of cinchona, producing more than 20,000,000 pounds of bark a year—what amounted to probably the most effective crop monopoly of any kind in all history.

Quinine, the alkaloid, was prepared commercially in Philadelphia in the United States as early as 1823[13] and has been prescribed therapeutically in this country ever since. The use of prophylactic quinine was advocated in this country as early as 1844[17] and was employed successfully among negro slaves during the construction of the Charleston and Savannah Railway.[15]

The introduction of cinchona bark into Europe enabled Morton in England in 1697 and Francesco Torti in Italy in 1712 to suggest that the paludic fevers could be separated from all others, not only by the typical periodicity (which was not evident in all cases) but also by their favorable response to cinchona bark treatment.[9]

Today the Japanese control all the cinchona of the Netherlands Indies and, with their Axis partner, Germany, they also control the Dutch stocks of cinchona alkaloids, together with the quinine factories. Consequently, we are once again dependent on American bark. In this hemisphere there has never been the intensive development of cinchona plantations with emphasis on varieties having a high quinine content. American barks generally have a relatively low quinine content but are reasonably rich in other principal alkaloids. Since all of these alkaloids have antimalarial value it has been decided to utilize American bark in the form of *totaquine,* which is a standardized antimalarial mixture of the alkaloids. This mixture was recommended by the League of Nations Health Organization in 1932. As now standardized in this country in the present emergency, it contains not less than 7 per cent and not more

than 12 per cent of anhydrous quinine, and a total of not less than 70 per cent or more than 80 per cent of the four principal alkaloids of cinchona. Totaquine, which will be the only form of cinchona available for civilian use in this country, is as effective as quinine sulphate when total daily doses are 20 grains or more. In smaller doses 7½ grains of totaquine have about the same therapeutic effect as 5 grains of quinine.[18,19]

ETIOLOGY

The Greeks and Romans, as noted above, from earliest days had associated malaria with bogs and pestilent vapors. In Italy it was a common belief that bad air from marshes was the actual etiologic factor and during the seventeenth century it became customary to say that patients dying from intermittent fevers had died from "the air" *(d'aria)* or from the bad air (*male aria*). At first, not the fevers, but the causes of the fevers were referred to in this way. But in time this expression came to be applied to the disease itself. So far as one can determine, Horace Walpole, in 1740, while in Italy, was the first to put the two Italian words together in print as one English word, "*malaria*," in a direct reference to the fevers of Rome (Oxford English Dictionary).

The word "ague" had been used in England and our own South as a name for the intermittent fevers. It is true that "*ague*" did not always refer to malaria, but the following reference indicates that it often did. William Grant, in his work entitled, *Fevers Most Common in London*, printed in 1771, stated (p. 453) that "a true ague is to be distinguished from every other fever by two symptoms; first, the *frigus*, *rigor*, and *horror febrilis* at the beginning of every fit; and secondly, an absolute apyrexia between the fits."

During the nineteenth century the concept of specific pathogenic microörganisms was established on a sound basis and it was natural that men should begin looking for a malaria germ. Because of the long established association between marshes and malaria, scientists began searching in marsh water and marsh air for this elusive pathogen. In Italy, for instance, "human guinea pigs" drank marsh water and allowed it to be injected as enemas or in nasal sprays—without proving anything.

In 1847, Heinrich Meckel, a German scientist, was studying organs and blood from a patient who had suffered from malaria. He noticed in some blood vessels of the brain certain round, ovoid, or spindle-

shaped protoplasmic masses containing black, irregular, *pigment granules* hitherto undescribed, although Lancisi in 1716 and Bright in 1831 had noted the graphite pigmentation of spleen and brain seen, *post mortem*, in malaria. From Meckel's carefully worded description it is clear that actually he was looking at pigmented malaria parasites but, at that day and under the circumstances, it is not surprising that he failed to realize their significance.[20]

Others, including Rudolf Virchow, founder of cellular pathology, also saw and reported this pigment *post mortem* and it came gradually to be associated with malaria. But no one suspected that the "pigmented globules" were parasitic organisms, although Planer in 1854 had seen them in a drop of fresh blood from a malaria patient.[20]

In 1876, Doctor Joseph Jones,[21] Professor of Chemistry and Clinical Medicine, University of Louisiana in New Orleans, stated that he had been making chemical and microscopical studies of the blood of fever cases for twenty years and that he was able to distinguish clearly the changes induced in the blood by malaria. In fact, he was able in a medico-legal case to testify that certain stains on the coat and shirt of the accused were not paint as suggested but were due to the blood "of a human being who had suffered and was probably suffering at the moment when the blood was abstracted, with malarial or paroxysmal fever." Jones described the characteristic pigment and stated that "many of the particles of the melanemic pigment were spherical, others irregular and angular, some entirely free, *others incased in a hyaline mass*. . . ." (italics not in original). He was undoubtedly describing malaria parasites.

Laveran

In 1878, Charles Louis Alphonse Laveran, a French army surgeon stationed at the military hospital in Constantine, Algeria, began an investigation of changes produced in the human body by malaria. His attention was naturally directed towards the pigment, now called hemozoin, which had aroused discussion and he searched for it not only in autopsy tissue but also in blood from patients. Working with inferior lenses (he actually used a 4 mm. dry lens) Laveran strained his eye many an hour over objects which did not seem to be normal blood cells but which he could not be sure were parasites. Persistently, he continued his studies and finally, one memorable day, 6th November

1880, in a wet smear of fresh blood, he saw unmistakable waving, hair-like projections or *flagella,* suddenly develop from one of the "pigmented spherical bodies" which had been puzzling him. Now, at last, he was certain that he was observing a living organism, a parasite in human blood. He named it *Oscillaria malariae.*

Laveran had talent and perseverance to follow up his observation and thus was able to reveal the minute cause of malaria. He saw ameboid, rosette, spherical, crescentic, and flagellate stages, but did not realize the relationship of these forms. Later he wrote four treatises on paludism, between 1884 and 1898, and in 1907 he was rewarded with a Nobel prize for his exceedingly important discovery of the malaria parasite.

Although a colleague, Dr. E. Richard, confirmed Laveran's discovery in Phillippeville, Algeria, in 1882, yet both announcements were received with well-nigh universal skepticism for several years. In 1885, however, Ettore Marchiafava, Italy's leading pathologist, and Angelo Celli, a colleague, saw the parasites in fresh blood behaving as Laveran and Richard had described and they became as enthusiastic in support as they had been in opposition. They were able to sketch, for the first time, part of the developmental cycle and they gave the organism its generic name of *Plasmodium.* Another Italian, Golgi, also in 1885, observed multiplication of the parasite by asexual spore formation and he noted that the patient's temperature rises when these spores are liberated. Councilman and Abbott, in the United States in the same year, also confirmed the discovery. Then, in 1891, in old St. Petersburg, Romanowski developed a new method of staining blood smears. This has been of the greatest usefulness in all subsequent studies of malaria parasites.

Early Theories

Many years before this discovery of malaria plasmodia numerous observers, "puttering around the springs of science," had suspected that mosquitoes might transmit malaria. For instance, Giovanni Maria Lancisi, a Roman and the greatest Italian physician of his time, in 1717, published a notable treatise on swamp fevers in which he suggested that since malaria disappears after drainage it is due to some sort of poison from marshes, possibly transmitted by mosquitoes. He studied these insects and concluded that they "inoculated their own bad hu-

mours into our blood." Then Lancisi planned a drainage scheme for marshy regions and remarked, "It is better not to fall ill than to be cured."

In 1807, Dr. John Crawford, a native of Ireland, settled in Baltimore, published an article in the Baltimore *Observer* on the "Mosquital Origin of Malarial Disease." Then in 1848, Josiah Clark Nott, a native of South Carolina, published the suggestion that not marsh vapors but the mosquito of the lowlands was the probable carrier of malarial fevers.

The clearest statement of such speculations was read before The Philosophical Society of Washington in 1882, and published in 1883, by Albert Freeman Africanus King,[22] an Englishman who went to America as a boy, studied medicine and practiced for nearly fifty years in Washington. King listed nineteen reasons why he believed that mosquitoes were the real source of malaria. In a footnote he stated that most of his reasons "were quoted from a paper read by Dr. John T. Metcalfe, United States Sanitary Commission, 1862." Metcalfe's article was published in 1863 under the title, "Nature and Treatment of Miasmatic Fevers." Reference to this publication makes it clear that the author brilliantly marshalled a series of basic observations about the epidemiology of malaria. But there is no mention of mosquitoes in Metcalfe's paper. King quoted most of Metcalfe's points and showed how well in each case his own mosquito theory would apply.

As King himself said, "While the data to be presented cannot be held to prove the theory, they may go so far as to initiate and encourage experiments and observations by which the truth or fallacy of the views held may be demonstrated, which, either way, will be a step in the line of progress." The records do not reveal a single experiment resulting from King's paper.

Manson's Theory

Patrick Manson was a Scotchman born in Aberdeenshire in 1844. From 1866 to 1871 he was Medical Officer of the Chinese Imperial Maritime Customs in Takao, Formosa. The next thirteen years of his life he spent in Amoy, China, practicing medicine, still under the auspices of the Customs Service. There he became very much interested in filariasis, a malady common in some tropical areas. While on leave in London in 1875, Manson searched medical libraries to find out what he

could about this disease. He learned that microscopic immature worms called *microfilaria* had been seen by Demarquay in 1863, by Wucherer in 1866 and 1868, and by Lewis (in blood) in 1872. Manson went back to Amoy in 1876, carrying along a new microscope, and he proceeded to study filariasis. It was natural that he should reflect on the question as to how the filarial worm could infect one man from another. He concluded that since the larvae were usually in blood they might escape with the aid of blood-sucking insects. He selected mosquitoes as being most probable because he thought their geographical range coincided with that of the disease.

His theory enunciated, Manson proceeded to feed mosquitoes on patients in whose blood there were embryo filarial worms. He then demonstrated these worms inside mosquito stomachs, where he saw that some were not digested but actually began to develop. Manson succeeded in tracing the filaria through the stomach-wall of the mosquito into the abdominal cavity, and then into the thoracic muscles. During this passage the parasite increased in size, developing a mouth, an alimentary canal and other organs. Quoting Manson, "Manifestly it was on the road to a new human host."

Here at last, scientifically observed, was a parasite of man's blood being sheltered in the gut of a blood-sucking insect, undergoing essential development, "*on the road*" to another human host. Manifest indeed were the implications of this discovery, first published in 1877 in the China Customs Medical Reports. Manson published again in 1879, using the title, "On the development of *Filaria sanguinis hominis*, and the Mosquito considered as a Nurse."

A few scientists accepted Manson's report with enthusiasm but many were cold to it, so the observations were repeated and amplified and republished in 1884 in the Linnean Society's Transactions.

Unfortunately, Manson believed that the filarial worms escaped from drowned mosquitoes into water which then infected the men who drank it. He had placed too much dependence in a book on natural history which stressed the ephemeral character of mosquitoes, leading him to believe that they quickly perished in the water on which they laid their first eggs. The fact that mosquitoes could live for several weeks, repeatedly taking blood and laying eggs, noted by Ross in 1897, was unobserved by Manson. The complete chain of filarial infection from man to mosquito to man was not demonstrated until 1899, when

Low found the worm in the proboscis of mosquitoes. He published in 1900 and his important discovery was soon confirmed by James.

Other scientists had already reported that parasites may in fact exchange one host for another. About 1858, Rudolf Leuckart discovered living in a small water flea called *Cyclops*, a worm which at one stage of its life is a parasite of fishes. This was probably the first instance when a member of the phylum Arthropoda, to which the insects as a class belong, was seen to be an intermediate host to a parasite of vertebrate animals. Again Leuckart, in 1867-68 observed, in the "meal worm" larvae of certain small beetles, a parasite previously known in the intestines of mice. About the same time Melnikoff, a Russian student working with Leuckart, found that biting lice can act as hosts to dog tapeworms. Here were the first cases known of insects acting as intermediate hosts to animal parasites.

The first time an arthropod was found acting as host to a parasite of man was in 1869 when Fedschenko, a Russian naturalist and traveler, prompted by a suggestion made by Leuckart in 1858, saw in *Cyclops* some embryos of the guinea-worm which parasitizes man. Fedschenko did not complete the cycle by infecting man again.

Then came Manson, in 1877 to 1879, with his observation which marked the first time an insect (mosquito) had been seen to act as an intermediate host to a parasite (filaria) of man. Manson's observations did not complete the man-to-mosquito-to-man cycle in filariasis but they gave him a logical basis for theorizing about malaria and mosquitoes. He formulated a working hypothesis based on facts observed by himself or published by others. This mosquito-malaria hypothesis he stated publicly in some lectures in 1894 (*Brit. M. J.*, Dec. 8, 1894). Briefly, Manson saw no reason why if mosquitoes could suck worms out of man's blood they might not draw out malaria parasites as well. He had been impressed by seeing in fresh blood smears the same unexplained exflagellation which had been noticed by Laveran. He asked himself, "why should exflagellation occur only *after* blood is drawn and never in the patient's body?" He surmised that this was for the purpose of infecting some kind of suctorial insect, most likely the mosquito. He thought, as he had about filariasis, that perhaps the mosquito later died, liberating the parasites in water which, when a man drank it, gave him malaria.

Shortly before Manson published his mosquito theory of malaria

transmission, Richard Pfeiffer enunciated in 1892 a logical conjecture of the same sort, based on some of his own studies with a related parasite. Said he, "The following solution suggests itself, but I bring it forward only as a hypothesis, the justification for which rests in the fact that it indicates a line of investigation. It is possible that in the case of the malarial parasite there exists a developmental cycle which completes itself outside the human host, possibly in the body of a lower animal (as, for instance, certain insects). This malarial germ could then be conveyed to man through the air or water or as Robert Koch has remarked to me through the sting of a blood-sucking insect."

So there was nothing fantastic about Manson's hypothesis. But human nature once more asserted one of its most ancient and deathless characters and Manson was derided for his speculations. His critics, some of them men of importance in the scientific world, called him "Mosquito Manson," and once on St. James Street, London, derisively tapped their foreheads as he passed by their club. Manson cheerfully tapped his own at them and walked on to Fame.

Smith and Kilborne's Demonstration

Between 1889 and 1893 Theobald Smith and F. L. Kilborne, Americans, proved the thesis that insect-like creatures can transmit disease from one animal to another. This work was first announced in the 6th-7th Report of the United States Bureau of Animal Industry in 1891, and was published *in extenso* as Bulletin No. 1 of this bureau in 1893. In some nicely planned, thoroughly scientific experiments, they demonstrated that ticks certainly transfer the cause of redwater, or Texas tick fever, from one cow to another. Ticks, they also found, could even inherit infection from a parent tick and pass it to a cow.

Manson had paved the way by showing that an insect could take an animal parasite out of the blood stream and act as a host to it. He failed to show that the insect could directly infect another man with this parasite. Smith and Kilborne went farther by observing that a specific pathogen could be carried from one animal to another by ticks. Although they appear not to have seen the actual parasite within the ticks, yet their experiments revealed for the first time a continuous chain of infection which included an *interlinking arthropod*. They were first to demonstrate that an arthropod can be an intermediate host to protozoan parasites of animals.

The Observations of Bruce

In 1896 David Bruce, a British Medical Officer working in Ubombo, Zululand, on a devastating disease of horses and cattle, called nagana, demonstrated, with the aid and comfort of Mrs. Bruce, that tsetse flies can carry the trypanosome parasite from animal to animal. Sheltered only by a wattle and daub hut, living on the roughest of food, sixty miles from other white folk, Bruce and his wife carried out experiments which were clear-cut and convincing. Bruce did not show and, not until 1909 was it demonstrated, that the tsetse fly is a true host rather than simply a mechanical carrier. Yet it seems fair to say that Bruce was the first to prove that a disease caused by a protozoan parasite can be transmitted by a true insect.

Ross's Discovery

In spite of all these advances, no one paid much attention to Manson's malaria theory until there came along Ronald Ross, another Scotchman, and an Army surgeon in the Indian Medical Service. Although Laveran had discovered malaria parasites in 1880, his drawings were not too good and in spite of repeated attempts Ross had not seen the organisms until Manson showed them to him in a London hospital, in 1894. Ross became interested in Manson's mosquito theory of transmission and went back to India to test it by actual experimentation. It seems incredible but there is no evidence that anyone else in the world was actively investigating the mosquito theory of malaria at that time.

Ross tackled the hypothesis seriously, commencing on his birthday, May 13, 1895. After much research, involving many mosquito dissections, Ross in Secunderabad on "Mosquito Day," August 20, 1897, first saw a pigmented malaria parasite from man, growing within the stomach wall of an Anopheles mosquito (*A. stephensi?*). This insect had fed exclusively on a patient whose blood contained crescents. Ross had no doubt that he was looking at the malaria parasite of man and it was certainly undergoing development in a mosquito. This observation crystallized the mosquito-malaria speculations of centuries!

By this time the fact was well established that multiplication of malaria parasites within red cells in the human body is entirely asexual. It was also known that not all of the young organisms so formed will, upon breaking out of red cells, complete a cycle by splitting asexually

at their own maturity. Some parasites called gametocytes, do not divide in this manner but take on unique shapes so that they may be recognized as distinct from ordinary asexual forms. Those of *P. falciparum*, for example, look like minute crescents. In 1897-98 William George MacCallum, an American pathologist, discovered the significance of these unique forms when he studied exflagellation. He found that the peculiar and sometimes crescent-shaped parasites in malaria blood, which do not split up, are actually male and female cells. MacCallum, in 1897, looking at *Haemoproteus*, a malaria-like parasite in a drop of crow's blood, and then MacCallum and Opie at Johns Hopkins in 1898 studying malaria organisms from man, saw male parasites exflagellate and then saw one of the flagella penetrate and thus fertilize a female parasite. There is no evidence that such mating ever takes place inside a living animal, but it may occur in a drop of blood on a glass slide and, as was soon discovered, it usually takes place in a mosquito's stomach. MacCallum and Opie's observations were of great importance for it became clear that malaria parasites have a sexual as well as an asexual cycle, and, taken together with Ross's observation, it was indicated that this sexual cycle probably took place outside the human body in the stomach of a mosquito.

Soon after Ross had made his first promising discovery in Secunderabad, he was transferred to a place where he was unable to experiment with malaria. This was unfortunate, but finally, through the influence of Manson and others who recognized the great importance of his studies, he was placed on special duty with instructions to investigate malaria in Calcutta. At that time, for various reasons, chiefly because of some riots due to antiplague inoculations, it was not possible for him to experiment with human beings, so, ingeniously, he used birds. In his laboratory he followed the parasite of malaria, stage by stage, in its development in the blood of sparrows. Then he allowed *Culex* mosquitoes to feed on the birds. Careful microscopic examination of these mosquitoes allowed him to study development of the parasites in the stomachs of the insects. He traced path and growth of the parasite as it made its way gradually from the mosquito's stomach to salivary glands. He then made his greatest discovery, something hitherto unsuspected either by himself or Manson. He found that mosquitoes that had fed on malaria infected birds and that had allowed the parasites to develop and to lodge in their salivary glands, could then infect healthy

birds. These in turn became malarious. So here was the last link! Bird to mosquito to bird. Thus, on July 9, 1898, he completed his demonstration of the entire life cycle of the parasite of bird malaria, which is transmitted by *Culex* mosquitoes. This was Ross's discovery and to no one else belongs the credit. It transcended far beyond Manson's hypothesis and it antedated the Italian contribution.

It was a tremendous and fundamental achievement for it was now perfectly clear that the closely related parasite of human malaria must probably in like manner be carried from man to man by mosquitoes. The first observation by Ross of a parasite of human malaria in the stomach wall of an *Anopheles* mosquito, followed by his absolute proof of the transmission of bird malaria by *Culex* mosquitoes, made it practically certain that mosquitoes transmit human malaria. However, it needed complete proof. Ross, having predicted the probable, set out to prove it. But he encountered initial difficulties and was soon ordered to investigate kala-azar, a subject he had not previously considered. In March, 1899, he left India and a few months later retired from the Indian Medical Service. He completed his original observation regarding human malaria in the same year in Sierra Leone.

The Italian Contribution

Ross, as a matter of course, had promptly reported to the world his work with bird malaria, as well as his original observation of a parasite of human malaria in the stomach wall of a mosquito. His bird experiments were confirmed by several observers, including Daniels, sent to Calcutta for this purpose in December, 1898, by the Malaria Commission of the Royal Society. In November, 1898, Amico Bignami, an Italian, succeeded in infecting a man experimentally with malaria by the bite of an *Anopheles* mosquito. Bignami and his colleagues, G. Bastianelli and Battista Grassi, a few weeks later, were the first to prove in full the cycle of the parasite of human malaria, and to show that human malaria is transmitted probably by only one genus of mosquito—*Anopheles*. These findings were quickly confirmed by Koch. In August 1899 the Sierra Leone malaria expedition, of which Ross was a member, found malaria parasites in two species of *Anopheles*.

To Italian workers must go praise for applying Ross's avian discoveries so quickly to human malaria. It should also be recorded, as noted by Shryock[23] that, just as the work of Theobald Smith and Ron-

ald Ross had stimulated the Italians, so in turn the Italians, through the medium of William S. Thayer, when he returned from Italy to Johns Hopkins, stimulated Walter Reed and his colleagues, who made the next great advance in the field of medical entomology by disclosing the vector of yellow fever.

To Ross is due, for all time, the credit of being first to place a scientific finger on mosquitoes as agents which spread malaria from man to man. This work brought him a Nobel prize in 1902, and later a knighthood from his King.

Dramatic confirmation of the fact that malaria is transmitted by *Anopheles* mosquitoes was furnished by Manson in 1900 in two simple tests. In the first experiment Doctors G. C. Low and L. W. Sambon and Signor Terzi, all of the London School of Tropical Medicine, lived in a screened hut during the three most malarious months at Fumaroli in the Roman Campagna. It was said at the time that it was sufficient during the fever season to sleep a single night there without protection to contract the disease. Yet these three men escaped. While the fact that they had no malaria was not absolute proof of its mosquito-borne nature yet, because their neighbors in unscreened houses suffered severely from malaria, the experiment was highly suggestive and was reported in scientific periodicals and newspapers throughout the world.

In the second and more convincing experiment, some infected *Anopheles* were sent by Professor Bastianelli on a three and a half day journey from Italy to London where there was no malaria. These mosquitoes had fed on a malaria patient in Rome. Manson's son, P. T. Manson, a healthy young London student, allowed himself to be bitten by three lots of these mosquitoes and fifteen days later he developed tertian malaria. The experiment was repeated by George Warren, laboratory assistant at the London School of Tropical Medicine. Some mosquitoes were still living after Manson's son fell ill, and, quoting Manson, Warren "thought it would be a pity to waste them, so he fed the insects on his own arm." He came down with tertian malaria fourteen days later. Both volunteers fortunately were cured with quinine. This experiment was significant even to the most skeptical.

Twentieth Century—First Quarter

During the first quarter of the twentieth century it was natural that interest in malaria should be centered around control measures based on

the newly demonstrated specific etiology. For malaria control had been an ancient and persistent hope. Records of empirical prophylaxis extend all the way from early centuries in ancient Italy to the late nineteenth century in the United States. For instance, one can cite Nerva, who in 96-98 A.D., was praised for his hydraulic works which improved Roman health because the water of his drains "removed the causes of bad air."[10] Some seventeen hundred years later, still in the empirical age, the transactions of the American Medical Association (1874) were largely filled with a symposium on drainage as related to public health and especially to the malarial fevers. This subject was first explored in the United States apparently in 1832, in the course of a medical survey of New York State.[15]

Mosquito nets were mentioned by Herodotus. They have been used ever since to exclude mosquitoes from sleeping individuals. For instance, in the middle of the last century the wife of the first Bishop in Capetown presented a mosquito net to David Livingston when he was in Central Africa. He responded with a charming letter which began as follows:[24]

14 July 1863

My dear Lady:

I feel exceedingly obliged by your kindness in making such a beautiful mosquito curtain for me. Beyond a doubt it is the handsomest that ever appeared in this country, and I am a great admirer of the invention . . .

Wire screen cloth for use in excluding mosquitoes and other flies was manufactured in the United States as early as 1865.[15]

Larvicides date back to about 1793, when oil (probably whale oil) was used in Philadelphia rain barrels to kill mosquito larvae.[15] Howard,[25] in 1892, was one of the first to use petroleum oil for this purpose. Dust larvicides such as Paris green were apparently not used against mosquito larvae until about 1920.[26,27]

The technique of warfare against mosquitoes developed rapidly after Ross disclosed the fundamental etiology. Indeed, Ross himself in 1899 in Sierra Leone carried out the first antimalarial work based on his own discovery. It is notable that Ross later wrote: "My work had been done not at all for the sake of parasitology, but in order to find a method for reducing the incidence of malaria amongst the inhabitants of warm countries." His prime interest remained, to the end, malaria control.

Outstandingly successful antimalaria projects in the first quarter of the century, included besides those mentioned below, that initiated in Malaya in 1901 by Malcolm Watson, that by Oswaldo Cruz and Carlos Chagas in Brazil, and by Ronald Ross in Ismailia, to mention only three of many.

Staten Island

At the turn of the century Staten Island was not only malarious, but also had an uncomfortably high density of pest mosquitoes. In 1901, Dr. Alvah H. Doty, Health Officer of the Port of New York, found that in one section of Staten Island 20 per cent of the inhabitants had malaria. He also discovered that the problem was twofold—pest mosquitoes breeding in salt marshes and *Anopheles* mosquitoes breeding in collections of fresh water, inland. Doctor Doty himself one evening collected twenty-two mosquitoes in a house, and found more than half to be anophelines, while on the opposite corner there was a patient with acute malaria.

A fairly large-scale antimosquito campaign was planned and carried out effectively in Staten Island under the direction of Dr. Doty and with help from the Department of Health of New York City.[28]

Although there is no reference to this project in Winslow's biography of Biggs, the following statement[29] has significance: "The New York City Health Department [of which Biggs was General Medical officer] from 1902 to 1913 was in large measure the concrete expression of the mind of Hermann Biggs; and the history of its development is the history of the progress of his sanitary statesmanship." It is also made clear in this biography that Doty and Biggs were close friends (indeed Doty was best man when Biggs married in 1898). Therefore, it seems not unreasonable to suppose that, in this Staten Island malaria and mosquito pioneer control project, one of the earliest, and one of the most effective of the early campaigns, in the United States, inspiration and advice stemmed from the great sanitarian we are honoring tonight—Hermann Michael Biggs.

Except for this work in Staten Island, and in one or two other areas, as in New Jersey, Long Island, and California, this country was slow to react until the Panama project had dramatized the subject of malaria control. Intensive malaria control in the South began with practical demonstrations in 1912-1916 in North Carolina, Virginia, and Missis-

sippi by Henry R. Carter and R. H. von Ezdorf of the U. S. Public Health Service, and, in coöperation with the International Health Board, at Crossett, Arkansas, in 1916.

During the World War in 1917-18 the Public Health Service carried out an extensive extra-cantonment, and the Army an intra-cantonment antimalaria program in fifteen states over a total area of 1,200 square miles. This very successful project not only protected considerable numbers of troops but it also demonstrated malaria control in a practical way and resulted in the training of a large personnel. In the years from 1919 to 1922 The Rockefeller Foundation, coöperating with the Public Health Service, demonstrated that malaria control in the South could be done for from 75 cents to a dollar per capita, with maintenance costs of 25 cents a year, about one quarter of the average yearly malaria payments per capita for quinine, doctors, and undertakers. These experiments proved that malaria control by antimosquito measures in the South was not only economically feasible but a sound business proposition.

Gorgas

The greatest early twentieth century demonstration of the usefulness of mosquito control measures was furnished by William Crawford Gorgas, who like Laveran, Bruce, and Ross, was an Army medical officer. In the words of Sir William Osler, "There is nothing to match the work of Gorgas in the history of human achievement." Not only did Gorgas completely control yellow fever by anti-*Aedes* measures (following the work in Cuba of Finlay, and of Walter Reed and his colleagues, which disclosed the vector of epidemic urban yellow fever) but, as the result of his *Anopheles* control, the malaria rate in Havana was reduced from the figure of 909 per thousand in 1899, to 151 in 1901, 44 in 1904, and 19 in 1908.

Because of his outstanding success in Cuba, it was natural that medical authorities should suggest that Gorgas take charge of sanitation during construction of the Panama Canal, where yellow fever and malaria had turned engineering efforts into shambles. Mosquitoes, at that time not yet unmasked, had administered to man the greatest engineering defeat ever known. The French losses in eight years were over 200 million dollars and 50,000 lives!

When the United States undertook to build this canal, Gorgas was

put in charge of the Sanitary Department of the Canal Zone by The Surgeon General of the Army. He was aided by an exceedingly capable Chief Sanitary Inspector, Joseph A. Le Prince, by the brilliant laboratory studies of Samuel Taylor Darling, and by the outstanding assistance of Henry Rose Carter, of the U. S. Public Health Service.

The *Anopheles* carrier in Panama bred in ponds, marshes, swamps, and standing water. The problem of controlling this widespread rural insect was much greater than that of controlling *Anopheles* breeding in Havana. The malaria rate in the Canal Zone in July, 1906, was equivalent to 1,263 hospital admissions per year per 1,000 of population! But Gorgas, with his unusually efficient sanitary organization and inspectors, reduced the numbers of canal workers admitted to hospitals for malaria from a yearly rate of 821 per 1,000 in 1906 to 76 per 1,000 in 1913. This work by Gorgas, with his concomitant success against yellow fever and dysentery, was a superb accomplishment, described by Sir Malcolm Watson as "the greatest sanitary achievement the world has seen."

If it be assumed that without Gorgas and his sanitary victories the occurrence of disease among our employees would have paralleled that among the French employees, who were without such help, then it can be stated that Gorgas saved the United States some 39½ million man-days of illness between 1904 and 1914, and not only so but he prevented some 71,000 deaths in the ten years of canal construction. Gorgas himself estimated that the sanitary work on the isthmus during the ten years of construction saved the United States some 80 million dollars, if indeed the canal could have been built at all in the presence of such intense malaria and yellow fever as that experienced by the French.[30]

It is easy to forget and time rapidly dims even the brightest records. Hence, it does not seem amiss to recall once more the tremendous world-wide impression made by the sanitary victories in Havana and Panama. For instance, when Gorgas visited London in 1914 he received, according to Osler, the greatest ovation ever given a medical man in England. Oxford University held a special convocation to confer upon him the honorary degree of Doctor of Science. At home, the President made him Surgeon General of the Army, and The Congress about a year later made him a Major General, at that time an almost unprecedented rank for a medical officer. He served his country with distinc-

tion in this high office during the World War. After retiring from the army in 1918, at the age limit, he went to South America as director of a yellow fever commission, under the auspices of The Rockefeller Foundation.

In 1920, in London, Gorgas became ill and was taken to the Queen Alexandra Military Hospital. There he was knighted by George V, receiving from the King's hand the insignia of Knight Commander of the Most Distinguished Order of St. Michael and St. George. A few days after receiving this knighthood, Gorgas died and was given the funeral of a British Major General in St. Paul's Cathedral, the highest honor that Britain could bestow. Later, his body lay in state for four days in Washington, and at the Church of the Epiphany an illustrious assembly gathered to pay last respects to this man whom the *Lancet* called "the best known and most uniformly successful medical administrator not of his age alone but of any age."

The Present

In this second quarter of the twentieth century malariology has shared in the general advance of science. It is not possible here to do more than to cite three notable lines of progress.

The Synthetic Antimalarials

Paul Ehrlich found, in 1891, that methylene blue will stain malaria parasites and he hoped that it would therefore act therapeutically by damaging the parasites in human blood. When its chemotherapeutic action was found to be slight, investigators modified its chemical structure, hoping to enhance the plasmocidal effect. This line of study finally led by devious paths to the synthesis of *plasmochin*, in 1924, by Schulemann and his colleagues in Germany, and of *atabrine* in 1930 by Kikuth, Mietzsch and Mauss in the same place. Neither of these drugs is synthetic quinine. Plasmochin is a quinoline derivative. Atabrine is a yellow dye derived from acridine. Plasmochin was found to be unique in its effectiveness against gametocytes, especially those of *P. falciparum*, and in its relative ineffectiveness against the schizonts of this same species. Atabrine was found to resemble quinine in its action against all species of schizonts and in its weakness in affecting any of the gametocytes. Quinine, plasmochin, and atabrine are alike in their inability in a percentage of cases to cure without the occurrence of relapses,

and in their failure, in safe doses, to prevent infection by sporozoites. None of the three has been found to be a true causal prophylactic, although each in small doses tends to suppress clinical symptoms. All three may exhibit toxic effects, quinine least and plasmochin most often.

Atabrine is by no means a perfect substitute for quinine but it is, nevertheless, a fairly effective antimalarial, now (fortunately) being manufactured on a large scale in the United States, England, and Russia. The Germans also are using extensively tablets of their own manufacture.

There is still no drug which is sufficiently effective to justify the use of chemoprophylaxis to eradicate malaria from communities. However, in spite of the fact that neither plasmochin nor atabrine has proved to be that potent chemical wand so earnestly desired, yet these drugs do represent a notable forward step in malaria therapy.

Pyrethrum Spray-Killing

There is a chrysanthemum indigenous to Dalmatia, growing in the fields like a small yellow daisy. The full blown flower of this plant contains active principles, called pyrethrins, which are deadly to insects. This latter fact has been known for many years in agriculture and public health and the dried pyrethrum flowers have become an important item of trade, so that large pyrethrum plantations have been developed in Japan, Kenya, and lately, in India.

Pyrethrins are contact poisons to which the cuticle of a mosquito is permeable. The toxic effect is seen chiefly in a destructive action on the central nervous system.[31] Kerosene extracts of pyrethrum have long been in household use against mosquitoes but only recently has it become apparent that pyrethrum spray-killing in many rural tropical areas is the best weapon available for malaria control, in fact it is the only one which is financially feasible in much of the rural tropics. Standard use of larvicides or of drainage and filling, or of screening has been far beyond the pocketbooks of these areas.

If the adult malaria-carrying mosquitoes of a community can be destroyed before they have lived long enough to become infective then malaria transmission in that community ceases. In villages where the malaria vector mosquito species tends to remain inside huts, cowsheds or outbuildings accessible to spray-killing, it is possible by spraying thoroughly once a week with pyrethrum to break the chain of infection and

thus to control malaria, at a cost which is considerably less than the cost of malaria and is not beyond the economic potentialities of the tropics.

This is notable progress which may be further enhanced by newer methods of dispensing the spray.[32] In 1935 it seemed true to state about the tropics that, "so far as average rural areas are concerned, the problem of control is still unsolved . . . it appears that we have no economically feasible control measures."[33] In 1942, experiments in rural South India proved that the malaria chain can be broken, in typical small villages, at per capita costs around $0.08 per year, which are economically feasible even in India.[34]

Species Eradication

In 1930, Shannon, an entomologist on the staff of The Rockefeller Foundation, reported that he had found *Anopheles gambiae* in Brazil. This was of great interest because *gambiae* is a notorious African species. Apparently a fast French destroyer had taken this deadly mosquito from Dakar to Natal, and the stowaway had succeeded in colonizing in the New World.

By 1931 the species had spread 115 miles up the coast stimulating local antimalaria campaigns along conventional lines. These had some success and lulled the Health Department into a sense of complacency which was completely shattered in 1938 when *gambiae* caused what was probably the greatest epidemic of malaria ever seen in the Americas. During the first six months there were over 100,000 cases with at least 14,000 deaths.[35] It became apparent that the African invaders had colonized for more than 200 miles north and west of Natal. This African species threatened to invade all of northern Brazil from which it might push on into Central America, with devastating results.

Displaying great courage, the Brazilian Government decided to attempt not merely the usual antimalaria measures but an actual eradication of every *gambiae* mosquito in the country. This complete extirpation of a species of mosquito had never been accomplished in any land at any time. A poll of experienced malariologists would doubtless have judged it an impossibility, for *gambiae* has the habit of breeding in all types of water collections, large and small.

By presidential decree, in 1939, the Malaria Service of Northeast Brazil was created. It was organized as an anti-*gambiae* rather than

anti-malaria service. Under the guidance of Soper and Wilson, of the staff of The Rockefeller Foundation, this Brazilian organization, much of which had had years of training in anti-*Aedes* work, grew to be 4,000 strong, and was allotted total budgets of more than two million dollars. The whole infested area, and a little beyond, was divided into squares of workable size; an adequate control gang was assigned to each square; and there was simultaneous and meticulous application of Paris green to breeding places and of pyrethrum spray-killing to adult resting places. The result of this determined, systematic and overwhelming attack was what now seems almost certainly to have been the complete eradication of *gambiae* from northeast Brazil and thus from the New World. The last evidence of *gambiae* in this area was found on November 14, 1940. Since January, 1941, all anti-*gambiae* measures have been suspended; a large staff of trained men have been constantly combing the area and contiguous zones for *gambiae*, and there has been a standing cash reward for finding it. Not a single living *gambiae* larva or adult could be found in 1941 or 1942. (But some dead adults were found in an airplane from Africa in 1942, illustrating clearly the need for complete enforcement of the pyrethrum spray-killing regulation for all airplanes arriving in Brazil from Africa.)

This is a very great achievement, a sanitary triumph, which marks the start of a new era in the fight against malaria. Great though the cost of the Brazilian campaign, it was very much less than the toll which *gambiae* would have exacted in the long run had it been only curbed by usual antimalaria measures rather than extirpated by a new and bold technique. This success suggests similar possibilities in other parts of the world. It is no longer certain that the malaria-carrying mosquitoes of a country could never be exterminated.

With large numbers of men well-trained in mosquito and malaria control work returning from overseas after the war, with the need for progressive post-war public health planning, with a genius for organization, and with money, it is certainly within reason to believe that malaria, if not the last mosquito vector, could be eradicated from the United States.

The Future

There are certain trends in malaria research which may be taken as some indication of what the future may bring.

Antimalarials

For instance, there is a tremendous amount of chemical, pharmacological, and clinical research going forward at the present time in a determined and intensive search for an antimalarial chemotherapeutic agent which will not have the deficiencies of quinine, plasmochin, and atabrine. The need is apparent when it is recalled that not one of this trio will cure with certainty, not one is a true prophylactic drug, and not one is of much value in the control of community malaria. Clark and his colleagues[36] as an experiment, tried for ten years to control malaria in some Panamanian communities by means of these drugs. They concluded that it was impossible by mass treatments to reduce the parasites to a point where malaria transmission in a community was much lessened.

It seems reasonable to hope that a more effective antimalarial will be developed in the not too distant future.

Immunity

As the science of immunology develops it is probable that the immunity factor in malaria will assume more importance. Whether vaccines and serums will ever have a practical place in combating malaria is a matter for speculation, with some evidence that some day a way may be found to make them useful.[37,38]

Removal of Social Obstacles

Probably the greatest advance in the future will be the removing of some of the social obstacles which block rapid progress in malaria control. Surely, it is amazing that, with all of our laboratory and field knowledge of malaria and its anopheline carriers, with all of our potent weapons of oil and Paris green, screens and pyrethrum, drainage and water-manipulation, with brilliant examples of successful projects, with our repeated demonstrations that it is cheaper to control malaria than to pay the economic toll it exacts from its victims—with all this, malaria control in the middle period of the twentieth century is still such a feeble effort. Is this due to insufficient knowledge, inefficient tools, paucity of funds? Or is our social organization unable to apply effectively the money, potential labor, existing weapons of control, and wealth of experience and research findings?

The answer to the question, "Why malaria?" seems to involve certain social obstacles to malaria control. Over widespread areas, particularly in the tropics, these appear to consist of such social facts as (1) a fundamental absence of educated and effective public opinion as regards the economic importance of malaria, the methods available for its control, and the community's responsibilities for its prevention; (2) a surprisingly limited use of sound administrative principles in public health, so that coördination and coöperation between departments does not exist, and continuity of effort in dealing with malaria is rare; (3) a lack of sufficient numbers of personnel specially trained in the entomological, agricultural, engineering, and public health phases of malariology; (4) a lack of cognizance by public officials as to the cost of malaria and the public benefit to be derived from its control; (5) a widespread ineptness in applying effectively and practically the results of research in malariology.[39]

What Bernal[40] wrote about science in general may be said of malaria control: "The obstacles to the solution of the problem are not any longer mainly physical or biological obstacles; they are social obstacles." It seems incredible that malaria still can be so great a scourge, for it is a preventable disease regarding which we possess as complete knowledge as for any human malady. The literature on malaria stretches back 2,000 years, grows actively, and has become enormous. There have been devised potent weapons for treatment and control. But malaria persists, of all diseases today probably the most effective barrier to prosperity, contentment, and health. What a paradox! Man, with his incredible machines and his streamlined science, stricken each year in millions because he fails to outwit a mosquito carrying Death in its spittle!

REFERENCES

1. Stitt, E. R. *Diagnosis prevention and treatment of tropical diseases.* 6 ed. by R. P. Strong. Philadelphia, Blakiston, 1943.
2. Faust, E. C. *Personal communication,* 1943.
3. Nichols, J. B. Recent mortality from malaria in the United States, *Virginia M. Monthly,* 1942, *69:*681.
4. Vaughan, V. C. *Epidemiology and public health,* St. Louis, Mosby, 1923, v. *2,* pp. 541-623.
5. Watson, M. The geographical aspects of malaria, *Geographical J.,* 1942, *99:* 161.
6. Sinton, J. A. What malaria costs India, *Records Malaria Survey India,* 1935-1936, *5-6.*
7. Hehir, P. *Malaria in India.* London, Oxford Univ. Press, 1927.
8. Russell, P. F. and Menon, M. K. A malario-economic survey in rural South India, *Indian M. Gaz.,* 1942, *77:*167.
9. Ross, R. *The prevention of malaria.*

London, Murray, 1910.

10. Celli, A. *The history of malaria in the Roman Campagna from ancient times.* London, J. Bale, 1933.
11. Jones, W. H. S. *Malaria and Greek history.* Manchester (England), Univ. Press, 1909; and *Malaria, a neglected factor in the history of Greece and Rome.* London, Macmillan & Bowes, 1907.
12. Childs, St. J. R. *Malaria and colonization in the Carolina low country, 1526-1696.* Baltimore, Johns Hopkins Press, 1940.
13. Hogstad, A., Jr. The three hundredth anniversary of the first recognized use of cinchona, *Proc. Celebration of 300th Anniversary of the First Recognized Use of Cinchona,* 1931:1
14. Editorial. *Brit. M. J.,* 1942, *1:*299.
15. Haggis, A. W. Fundamental errors in the early history of cinchona, *Bull. Hist. Med.,* 1941, *10:*417; 568.
16. Boyd, M. F. Historical introduction to symposium on malaria, in *Symposium on Human Malaria,* Washington, Am. Assoc. Adv. Sc., 1941, p. 1.
17. Terry, R. J. Dr. John Sappington, pioneer in the use of quinine in the Mississippi Valley, *Proc. Celebration of 300th Anniversary of the First Recognized Use of Cinchona,* 1931: 165.
18. Field, J. W. Notes on the chemotherapy of malaria, *Bull. Inst. M. Research, Federated Malay States,* 1938, no. *2.*
19. Marañon, J., Perez, A. and Russell, P. F. Philippine totaquina, *Philippine J. Sc.,* 1935, *56:*229.
20. Thayer, W. S. and Hewetson, J. The malarial fevers of Baltimore, *Johns Hopkins Hosp. Rep.* 1895, *5:*1.
21. Jones, J. Medico-legal evidence relating to the detection of human blood, presenting the alterations characteristic of malarial fever, on the clothing of a man, accused of the murder of Narcisse Arrieux, Dec. 27, 1876, near Donaldsonville, *New Orleans M. & S. J.,* 1878-79, *6:*139.
22. King, A. F. A. Insects and disease—mosquitoes and malaria, *Pop. Sc. Monthly,* 1883, *23:*644.
23. Shryock, R. H. *The development of modern medicine.* Philadelphia, Univ. of Pennsylvania Press, 1936, p. 279.
24. Leikind, M. C. A note on the early history of the mosquito net, *Army M. Bull.* 1943, no. *65:*173.
25. Howard, L. O. *A history of applied entomology.* Washington, Smithsonian Miscellaneous Collections, 1930, v. *84.*
26. Roubaud, E. Emploi du tricométhylène en poudre pour la destruction des larves d'anophèles, *Compt. rend. Acad. d. sc.,* 1920, *170:*1521.
27. Barber, M. A., and Hayne, T. B. Arsenic as a larvicide for anopheline larvae. *Pub. Health Rep.,* 1921, *36:*3027.
28. Howard, L. O. Anti-malaria work in the United States, in Ross R. *The prevention of malaria,* New York. Dutton, 1910, p. 332.
29. Winslow, C. E. A. *The life of Hermann M. Biggs.* Philadelphia. Lea & Febiger, 1929, p. 185.
30. Gorgas, M. D. and Hendrick, B. J. *William Crawford Gorgas, his life and work.* Garden City and New York, Doubleday, Page & Co., 1924.
31. Wigglesworth, V. B. The effect of pyrethrum on the spiracular mechanism of insects. *Proc. Roy. Entomol. Soc. of London,* 1941, *16:*11.
32. Goodhue, L. D. Insecticidal aerosol production, *Indust. & Engin. Chem.,* 1942, *34:*1456.
33. Russell, P. F. Epidemiology of malaria in the Philippines, *Am. J. Pub. Health,* 1936, *26:*1.
34. Russell, P. F., Knipe, F. W. and Rao, T. R. A water emulsion of pyrethrum extract for spray-killing adult mosquitoes, *Indian M. Gaz.,* 1942, *77:*477.
35. Soper, F. L. and Wilson, D. B. Species eradication, *J. Nat. Malaria Soc.,* 1942, *1:*5.
36. Clark, H. C., Komp, W. H. W. and Jobbins, D. M. A tenth year's observation on malaria in Panama, with reference to the occurrence of variations in the parasite index during continued treatment with atabrine and plasmochin, *Am. J. Trop. Med.,* 1941, *21:*191.

37. Mulligan, H. W., Sommerville, T. and Swaminath, C. S. Cellular and humoral agencies in defence against malaria, *J. Malaria Inst. India,* 1940, *3*:563.

38. Russell, P. F. and Mohan, B. N. The immunization of fowls against mosquito-borne *Plasmodium gallinaceum* by injections of serum and of inactivated homologous sporozoites, *J. Exper. Med.,* 1942, *76*:477.

39. Russell, P. F. Some social obstacles to malaria control, *Indian M. Gaz.,* 1941, *76*:11.

40. Bernal, J. D. *The social function of science.* New York, Macmillan, 1939.

BRUCELLOSIS*

Diagnosis, Differential Diagnosis and Treatment

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THE opportunity to talk to this distinguished group on some aspects of brucellosis is a welcome one. That there are few subjects so neglected or so worthy of attention is slowly coming to be realized. What is needed however is a new and more complete conception of this illness of protean manifestations and numerous disguises. I cannot hope to give it to you fully in the necessarily limited time that is available, for it is not a small subject, even when restricted to diagnosis and treatment.

I am indebted to my superior officers in the Navy Department for their sufficient interest in scientific medicine to permit me to interrupt my tour of sea duty long enough to address you. This action does not imply official approval of the subject matter. The ideas expressed are my own and do not necessarily reflect those of the Medical Department of the Navy.

INDICATIONS FOR LABORATORY STUDIES

In deciding when it is necessary to employ the various diagnostic procedures for brucellosis in the study of an obscure illness the question of exposure is one that may well be, to a large extent, ignored. Brucellosis cannot be ruled out on the basis of lack of known exposure. Indeed, exposure to Brucella infection is comparable in its universality to exposure to tuberculosis. There are few persons who have never ingested raw milk or cream, or raw milk products, such as cheese, butter, buttermilk, or ice cream, or who have never been in contact with infected cows, horses, sheep, goats or hogs.

In children it is relatively easy to trace the feeding formulae in infancy, the subsequent diet and the contacts. If the child never had mother's milk, nor raw nor imperfectly pasteurized cow's or goat's

* Read March 19, 1943 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

milk; if it had none but pasteurized milk products; if it never came in contact with possibly infected animals—and if the story can be completely credited—then that child's exposure is unlikely. The use of certified milk exclusively, unless it is pasteurized, is no guarantee against milk-borne infection, however, for certified milk is not above suspicion if raw. The possibility of intrauterine infection or infection during passage through the infected birth canal of the mother cannot be dismissed lightly. Hagebush and Frei found in 74 per cent of 182 cases of childhood brucellosis, that the mother also had the disease. This might have been due to a common milk supply; however, four of the infants developed relatively severe symptoms and positive tests before nursing and before taking any other food except dried or evaporated milk formulae. Illness developed in from three to eight days after delivery. Similar instances have occurred among my patients and have been reported by others.

That Brucella grows more readily in cream than in milk is often overlooked in considering exposure. Patients often remark that they never use milk, but cream is almost universally used. Contact with cattle and other possibly infected domestic animals must also be considered. The laboratory worker must be classed among those exposed by direct contact, along with farmers, butchers, slaughterhouse employees and veterinarians.

It is not only the rural resident who is exposed through the medium of raw milk. There is a smug complacence among laymen and physicians alike, when the diagnosis of possible brucellosis is made in a patient who has been a lifelong resident of New York for example. The suspicion is likely to be dismissed as fantastic because the patient has used pasteurized milk and cream at home exclusively for the past twenty-five years, feeling that this somehow gives security against Brucella infection. There are but few of these persons who have not spent summers or brief vacations in the country where, knowingly or unwittingly, they have had raw milk. About 45 per cent of the herds in the United States have showed some degree of infection.

The death from acute brucellosis of a New York physician a few years ago illustrates the need for considering this infection in the absence of any known history of exposure. Just before death Brucella melitensis was recovered from a blood specimen. Then, as the result of keen thinking on the part of one of the attending physicians, the same

goat strain of Brucella was grown from an uneaten portion of Italian cheese found in the patient's apartment. Cheese had always been looked upon as innocuous.

Incubation period gives little or no help in diagnosis of infection as related to known exposure. The elapsed time from a single known exposure until development of evidence of active illness has been noted to be anywhere from a few days to several months. Even this is understatement, for clinically recognizable illness may not occur for years following exposure, the infection remaining latent or subclinical or subsiding to a chronic phase after a wrongly diagnosed acute illness.

It is therefore better to leave the question of exposure until later in the study of the patient and not to be influenced greatly by it; to consider the possibility of brucellosis and to do the various tests routinely in all obscure illnesses, acute or chronic.

My plea for more accurate diagnosis of this common illness would be bolstered if I could give you exact figures as to its incidence; as, for example, what percentage of all admissions to a large general hospital is represented by Brucella infection. At some later date I hope to gather this information through a study of naval personnel and their dependents. Gould and Huddleson estimated that about 10 per cent of the population of the United States had become infected and that about one per cent of that number were clinically ill. The incidence of infection is higher in rural communities but, if one is brucellosis-conscious, the evidence of its frequency among all groups is overwhelming. In the course of the last ten years of a practice largely devoted to internal medicine and consisting of urban and rural dwellers in about equal proportions, approximately 400 cases of brucellosis were encountered. Of these about 30 per cent were residents of New York and the metropolitan district. About 10 per cent were acute cases, the remainder chronic. For the previous ten years I had failed to recognize a single instance, having shared the usual impression that it was an acute illness of infrequent occurrence characterized by long-continued high fever, and diagnosed by the simple expedient of the blood agglutination test. In 1941, during my first six months of naval service, fourteen cases of brucellosis were diagnosed on my wards at the Brooklyn Naval Hospital. These were the acute infectious disease wards and therefore did not include the cases presumably admitted to other wards.

These are but some of the reasons for doing routine tests for brucel-

losis. Let us now consider the methods and the rationale for the performance of the multiple tests rather than place reliance on the blood agglutination test alone.

Diagnosis

There are four commonly used laboratory procedures: blood agglutination test, intradermal test, phagocytic index, and culture. The use of these tests, along with careful history and physical examination, usually furnishes adequate evidence on which to establish or rule out the diagnosis of brucellosis.

The Agglutination Test: This test is comparable to the agglutination test with B. typhosus. It is often negative in acute brucellosis however, and, in a probable majority of cases, is negative in the chronic illness. Therein lies the most frequent source of error in the diagnosis of brucellosis, next to the failure to consider the diagnosis at all. Most unfortunately it is almost standard practice to accept one or more negative blood agglutination tests as signifying the absence of Brucella infection.

To evaluate agglutination in a low titer (below 1:80) as negative is also wrong. Such results should be viewed as suggestive, pending further study. The absence of agglutinins does not mean the absence of infection. *Positive blood culture, in the presence of persistently negative agglutination tests, has been reported by Evans and others.* This cannot be emphasized too strongly.

The finding of Brucella agglutinins in low titer occasionally occurs as cross-agglutination due to infection with B. typhosus, B. tularense, or B. proteus X 19. Differentiation is usually easy through completion of the other laboratory procedures applicable to the various infections as well as for brucellosis. In tularemia, for example, agglutination may occur with Brucella abortus in a 1:20 or 1:40 dilution of the patient's serum but usually occurs in a higher dilution with B. tularense.

The presence of agglutinins in a titer of 1:80 or higher is presumptive evidence of Brucella infection, if occurring in a patient whose clinical findings are compatible with brucellosis. Agglutinins may persist for weeks or months after recovery but usually are fleeting.

Parenthetically I should add that negative blood agglutination tests in cows likewise are unreliable evidence of the absence of Brucella infection. Positive cultures of the milk of cows with persistently negative blood agglutination tests have been reported by several. It is for this

reason that I believe that certified milk should also always be pasteurized.

As evidence of the still-existing misconception of the significance of the blood agglutination test, as well as of too great faith in the likelihood of positive culture, I quote the following from Stitt: "Undulant fever obviously may be differentiated from trench fever by the detection of Micrococcus melitensis in the blood or by the agglutinating reaction of the blood with the organism." We are to understand from this that brucellosis is ruled out if culture and agglutination test are negative. To discuss agglutination test and culture for Brucella infection without mentioning the limitations of the tests is to add to the confusion already existing. It seems essential to add the qualification, "if positive," to a mention of either test since neither has any significance when negative.

It is essential to collect specimens of blood for the agglutination test prior to the performance of the skin test lest artificial agglutinins be formed in response to the intradermal antigen.

Phagocytic Index: Huddleson gave the name opsonocytophagic test to this procedure for the determination of the specific phagocytic power of the white cells, adapting the method to Brucella infection from technique in use in the study of other illnesses. Much controversy has arisen over its value. It has proved to be highly accurate in my work, both in diagnosis and as a criterion of progress in patients under treatment, although it has limitations. By itself it has little significance, which is surely what Evans meant when she said that it has the least value of the four accepted laboratory procedures. Her comment has been interpreted by some to mean that it is unreliable. When properly performed, on freshly collected blood, with meticulous technique, and when interpreted in the light of the result of the intradermal test and of clinical findings, it will be found to be invaluable. Performance of the test may be deferred for a week or even ten days after the skin test when circumstances make it necessary, without materially affecting the result.

The result may be reported as the numerical index of Foshay, graphically, as by Evans, as the percentage of cells showing marked phagocytosis, as the average number of bacteria contained in each white blood cell, or as the number of cells showing marked, moderate, slight and no phagocytosis, in accordance with Huddleson's method. This last method seems to me most informative; also the shift to the right or

left is easily visualized in comparing subsequent reports. The test should not be thought of as positive or negative but rather as showing high, moderate, little or no resistance.

In itself the phagocytic index indicates only the degree of opsonic activity of the blood toward Brucella. When accompanied by a positive skin test it does help greatly to distinguish between patients who presumably have recovered from old infections and those whose present illnesses are probably due to still active infection. The skin test, to be discussed shortly, must be performed before the diagnostic significance of the phagocytic index can be evaluated. If the skin and agglutination tests and culture all are negative we do not know whether or not the patient has ever had brucellosis and therefore the opsonic power of his white cells has no interpretable diagnostic significance.

If the skin test is positive we know that the patient has an old or a recent infection, of undetermined activity. If then we find a low phagocytic index, it is presumptive evidence that the patient has not recovered from that infection. If the positive skin test is accompanied by a high phagocytic index, it is presumable that the patient has recovered from that infection. Obviously, this information cannot be deduced in the absence of illness possibly referable to Brucella infection.

The test may not be interpreted to indicate cure or immunity, no matter how high the index, contrary to Huddleson's belief. Robinson reported the case of a patient who died of brucellosis with 100 per cent of his white cells showing marked phagocytosis; the blood culture was positive. The relative virulence of the organism must be considered. Also, what may appear to be immunity may change to a low level of resistance preceding or accompanying relapse within a few weeks, for opsonins, too, may be fleeting. So, in a small percentage of patients, the test is not helpful.

Blood for the opsonocytophagic test must be fresh. In my monograph I quoted Huddleson as stating that the procedure must be done before the blood is more than six to ten hours old. Lintz has subsequently pointed out that the phagocytic activity of the white cells decreases rapidly after the first or second hour. Therefore the test should be done on blood that is not more than three hours old.

The Intradermal Test: Use of a sensitive antigen and accurate interpretation of the skin reaction obviously are essential. Heat-killed Brucella abortus organisms seem to furnish the most sensitive and reliable

antigen. Brucellergin, derived from the filtrate of the three strains of Brucella, apparently is much less sensitive. In a series of tests in 168 patients, all of whom had drunk milk from an infected herd, Angle did intradermal tests with the heat-killed organisms on one arm and with Brucellergin on the other, simultaneously; he noted fifty-four positive reactions to the heat-killed vaccine and only twenty-seven to Brucellergin. Although he made no comment on its significance, other than to point out that the possibility of a slough at the site of the test is avoided by the use of Brucellergin, it is obvious that the question of sensitivity of the antigen is involved.

The test is done with 1/10 cc. of a killed bacterial suspension of 2000 million Brucella abortus organisms per cc. injected intradermally with a very fine, short needle, using the same technique as for the tuberculin test. The reaction should be read at the end of four days but, if apparently negative, should be kept under observation for another seven days. I first pointed out the importance of the delayed positive reaction in 1934; the observation has since been confirmed by others. A positive reaction may vary from a visible, palpable, reddened nodule at the site of the intradermal injection to a markedly reddened, indurated area with lymphadenitis and marked systemic reaction.

A weakly positive reaction has the same diagnostic significance as a violently reacting test. Both indicate that the patient at some time harbored or suffered from Brucella infection. The degree of local and general reaction, in addition, indicates the degree of sensitization to Brucella protein that has occurred. This is an aid in planning vaccine therapy when such is indicated. Also, the aggravation of existing signs and symptoms, clinically attributable to the illness, which so commonly occurs during the skin reaction, is of additional diagnostic significance. This is especially valuable information if, following the subsidence of the skin reaction and the clinical exacerbation, there is evidence of clinical improvement and a commensurate rise in the phagocytic index.

It is well to avoid the mixed strains present in commercial vaccine in doing the intradermal test, as well as in treatment. Most of them comprise abortus and melitensis or abortus and suis strains. They are no more accurate than the abortus strain alone, no matter what the infecting strain of Brucella, but *are* more apt to produce severe reaction, local and general, and a greater percentage of sloughs. The necrosis

occurring at the site of the intradermal injection in a small percentage of patients will be shown, along with various types of skin reactions, by means of a few kodachrome transparencies. The sloughs may be slow to heal and may leave some permanent scar but the information obtained is of sufficient value to justify use of the method.

A positive skin test alone should never be the sole evidence on which to base a diagnosis of brucellosis. Nor may a negative skin test be used to rule out brucellosis; positive blood cultures, in the presence of negative skin tests, have been reported by several.

The presence of positive skin tests in seemingly well persons has been quoted as evidence of the non-specificity of the skin test. That is, I believe, an inaccurate evaluation. Under such circumstances the finding is comparable to a positive tuberculin test in a well person, indicating old infection, quiescent or possibly actually cured.

Culture: The discussion of culture is left until last, not because of its lesser importance, but because it is the least likely of the four tests to furnish any positive information, especially in chronic brucellosis. It is the one definitive diagnostic measure, when positive, just as tubercle bacilli in the sputum furnish the only certain evidence of pulmonary tuberculosis. The various tests for brucellosis all must be correlated with each other and with the clinical picture, as I have reiterated deliberately. In the absence of positive culture from blood, urine, feces, sputum, bile, synovial fluid, or other exudate, discharge, or tissue, we may not rule out brucellosis until all other diagnostic and clinical study has been made. The cultural methods must be exact. It is only in the presence of acute infection, especially with the melitensis strain, that there is reasonable expectancy of recovering the organism, so difficult is it to grow. Although methods of culture have been improved, there seems little tendency on the part of laboratories to utilize these more accurate methods. Poston's technique includes the use of special media (liver infusion agar, bacto-tryptose agar, and others), the use of 5 to 10 per cent of carbon dioxide in air for the growth of the abortus strain, long weeks of incubation and transfers, and the keeping of inoculated guinea pigs for periods as long as eighteen weeks before studying them at autopsy. Poston studied fourteen patients in whom she suspected chronic brucellosis in spite of the completely negative multiple tests. Using her own technique she isolated Brucella from five of the fourteen patients.

The fact that cultural findings are usually negative should not dis-

courage their use, along with the other tests. In fact it should be a routine procedure in the study of all patients in whom brucellosis is suspected and in all other illnesses of an obscure nature. By way of example I will briefly quote the case of a young married woman who had three spontaneous abortions, with salpingitis and profuse purulent discharge accompanying convalescence from each abortion. Fever never was above 99.6. Blood agglutination with Brucella abortus occurred in a dilution of 1:40. I did not see her following the first occurrence. At the second abortion the placenta showed large areas of necrosis but was inadvertently destroyed before culture could be attempted. The placenta at the third abortion showed gross and microscopic areas of calcification but no significant cultural findings, perhaps due to the long delay in transit to the nearest good laboratory. Following this occurrence a specimen of uterine discharge, obtained from cervix and vagina by aspiration, after instillation of sterile glycerol, was sent by mail to the New York State Department of Health Laboratory, 135 miles distant. In spite of the delay, Brucella of the abortus-melitensis group was isolated.

Ordinarily it is essential that specimens for culture be very fresh, not more than an hour old, if cultural attempts are to have their best chance of success. It is too often the habit of laboratory technicians to allow specimens to stand about for hours before inoculating the proper media. In one instance a specimen of bile, obtained by duodenal drainage after considerable difficulty, was not sent to the laboratory until the next morning, but an utterly valueless report of no growth of Brucella was rendered in the routine way. I might add that at least a degree of enthusiasm for the work in hand seems particularly important in the study of brucellosis.

Differential Diagnosis

Brucellosis is becoming known as a disease which masquerades under as many guises as does syphilis. Its differential diagnosis obviously involves consideration of the innumerable diseases and syndromes which it is so apt to simulate. There will be time for discussion of but a few.

Pulmonary Tuberculosis: Pulmonary tuberculosis is one of the illnesses most frequently confused with brucellosis. Clinically, chronic or subacute brucellosis may so exactly simulate pulmonary tuberculosis that the patients are admitted to sanatoria without hesitation on the part

of staff examiners. If sputum is negative, if x-ray evidence is lacking or if there are atypical lesions, a presumptive diagnosis of tuberculosis is often made on the basis of productive cough, loss of weight, pleuritic chest pain, night sweats, fatigue, afternoon elevation of temperature, positive tuberculin test—and failure to consider brucellosis. Loss of weight, low grade fever and fatigue are, of course, very common in brucellosis. Occasionally the pulmonary lesions of brucellosis are indistinguishable from tuberculosis. Pleurisy is fairly common. Beatty has reported several instances of hemoptysis in brucellosis. If the multiple tests for brucellosis are done, most of the errors are avoidable. The coexistence of the two diseases presents a most complicated problem and is not infrequently encountered.

The chagrin of the superintendent of one of the best of the tuberculosis sanitoria at the reply made by a patient will probably be long remembered by all present. He had just completed the chest examination of a young woman at a follow-up clinic. "My dear girl," he had said, "you do not have tuberculosis. Whoever made such a diagnosis?" The patient had answered, "You did, Doctor. I spent six months in the sanatorium under your care." He had forgotten that he had made a clinical diagnosis of tuberculosis himself and had admitted her in spite of negative sputums and only suspicious radiographic findings. She had had a severe productive cough, pleuritic pain, low-grade fever, weight loss and secondary anemia, subsequently shown to be due to brucellosis during one of several exacerbations which followed.

A normal or low sedimentation rate, when present, is of great help in the differential diagnosis between active tuberculosis and brucellosis. In a small proportion of cases the sedimentation rate is also increased in brucellosis, however.

Peribronchial and hilar infiltration may be seen on routine chest x-ray in suspected tuberculosis. If associated with clinical and laboratory evidence of brucellosis and no evidence of tuberculosis; if there is found complete clearing at subsequent x-ray examination, with later recurrence accompanying relapse of brucellosis, there is adequate evidence that these are respiratory manifestations of brucellosis. Figure 1 illustrates this point. One young man had a recurrence of orchitis and epididymitis with each exacerbation of brucellosis which was also attended by lung involvement, with complete resolution between attacks.

Pneumonia: Figures 2 and 3 of two patients with lung involvement.

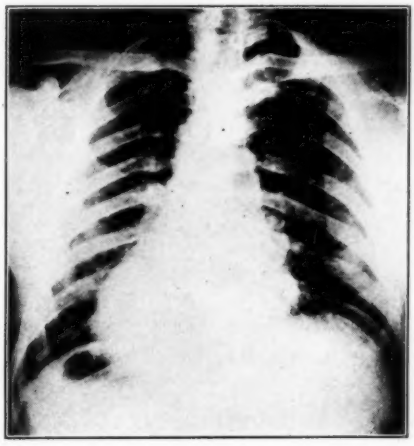

Fig. 1. Infiltration, middle third of left lung, during subacute relapse five years following severe, prolonged, typhoid-like Brucella infection. Orchi-epididymitis accompanying this and subsequent recurrences of pulmonary involvement, each attack subsiding promptly following specific vaccine therapy.

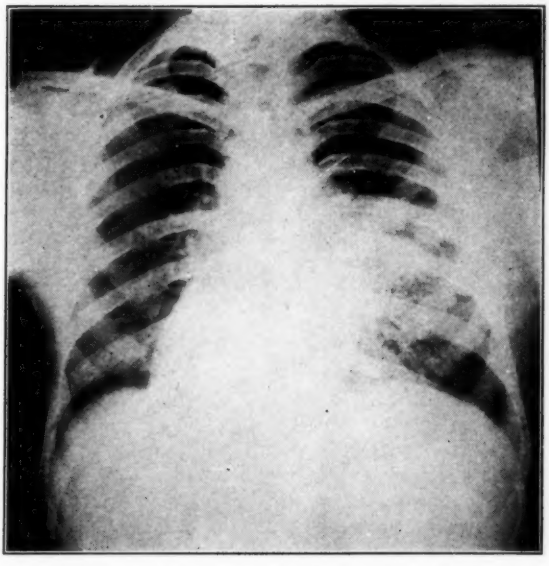

Fig. 2. Brucella lobar pneumonia in Maltese sailor; history of brucellosis in childhood; signs and symptoms similar to lobar pneumonia of other origin; slow resolution.

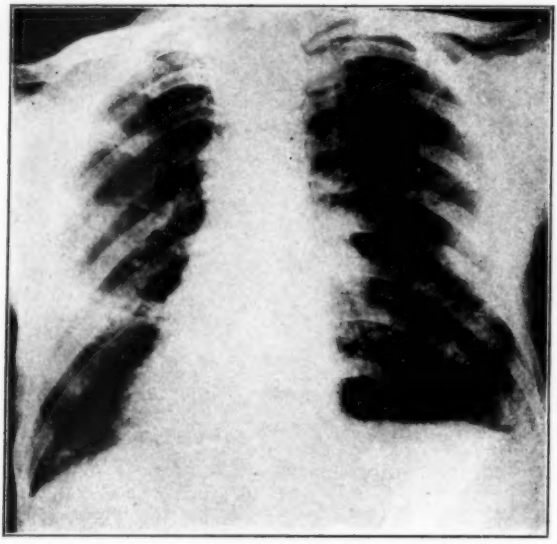

Fig. 3. Diffuse, severe, Brucella bronchopneumonia in Italian veteran; profuse, thin, muco-purulent sputum; slow, complete resolution.

seen at the Naval Hospital, illustrate the diagnostic value of radiography in brucellosis and the fact that brucellosis must be kept in mind whenever atypical findings are encountered. Brucella pneumonia is not of rare occurrence. Beatty has reported many cases. The organism was isolated from the sputum in two cases by Eyre. Lobar pneumonia due to Brucella often presents a radiographic picture similar to that shown in Figure 2, with a fan-shaped area of consolidation radiating from the hilum toward the periphery. The bronchopneumonic process shown in Figure 3 is not typical of Brucella bronchopneumonia but is, I believe, unique in its severity and diffuse distribution. Obviously this radiographic picture suggests miliary tuberculosis or miliary carcinomatosis as much as it does bronchopneumonia. Resolution was very slow, sputum thin and extremely profuse (averaging two large sputum cupfuls per day). There was ultimate clearing and recovery. There was no evidence of bronchiectasis. The first patient was Maltese, the other Italian. The Maltese sailor had lived in Malta and had had brucellosis in childhood.

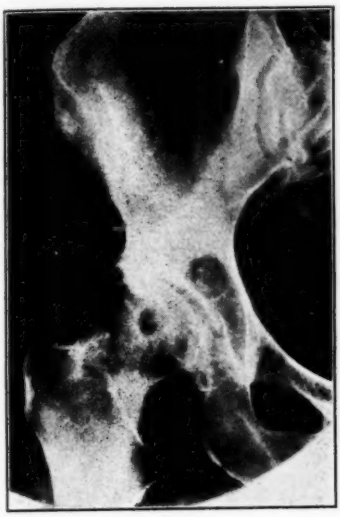

Fig. 4

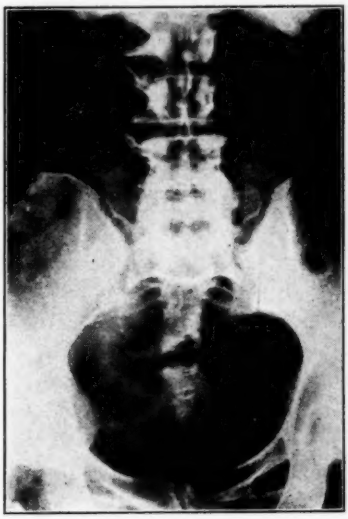

Fig. 5

Fig. 4. Hypertrophic arthritis and degenerative bony changes in brucellosis; good functional response to Brucella abortus vaccine.
Fig. 5. Brucella spondylitis; same patient as shown in Fig. 4.

Arthritis: Brucella infection must be considered in the differential diagnosis of arthritis. The infection has been shown to be a direct or indirect causative factor in some cases of all types of arthritis. Brucellosis should be routinely considered and careful diagnostic study made in all cases unless other cause has been demonstrated and successful therapy instituted. In communities where raw milk has been in general use an amazingly high percentage of the run-of-the-mill cases of arthritis have been found associated with brucellosis and responding to specific therapy of Brucella infection. By this I do not mean shock therapy. In one such community Goldfain reported an incidence of 50 per cent. The incidence is lower in urban communities. While it has never been accurately estimated, my own experience has shown that it is by no means negligible. Differentiation is difficult. Clinically there is little to distinguish Brucella arthritis from arthritis of other origin. As in other forms of brucellosis the condition is likely to be atypical to some degree, which should be the cue for thinking of Brucella infection. Any joint may be involved but quite often the involvement is bizarre, involving

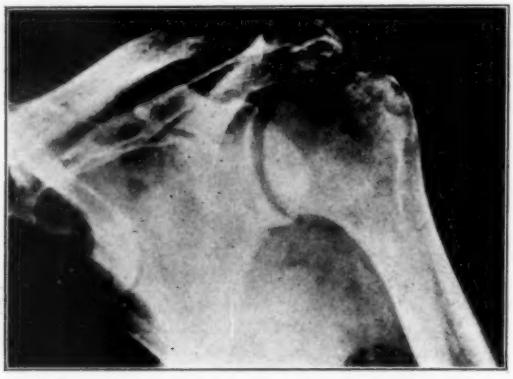

Fig. 6. Arthritis of shoulder and degenerative changes in head of humerus in woman of 68; complete functional recovery following Brucella abortus vaccine.

the metatarso-phalangeal joint of the great toe, as in gout, or the metacarpo-phalangeal joint of the thumb or several small joints limited to the medial or lateral half of one hand or foot. When involving knees, wrists or hips there is likely to be no clinical suspicion that one is not dealing with the usual types of atrophic or hypertrophic arthritis. Under all circumstances the differential diagnosis depends upon laboratory evidence that the patient has active Brucella infection and on response of the arthritic process to specific therapy. Obviously an unrelated arthritis may exist in patients with brucellosis. Therapeutic test doses of vaccine, if followed by improvement in the joint condition, with commensurate rise in the phagocytic index, furnish the best criterion in the absence of positive culture. Culture is most likely to be positive in intermittent hydrarthrosis and other acute or chronic joint effusions, especially of melitensis origin.

Figures 4 to 7 illustrate radiographic changes in these cases. You will see some changes, notably atrophic areas in bone, that are not usual in arthritis of other origin. All had positive tests for, and clinical symptoms of, brucellosis and all responded to treatment with Brucella abortus vaccine, without shock-producing reactions. Periarthritis of the shoulder joint is not infrequently encountered. It seems most likely to follow mild trauma in patients with latent or active chronic brucellosis.

Rheumatic Fever: In the acute joint manifestations resembling rheu-

Fig. 7. Hips and pelvis of same patient shown in Fig. 6, five years later; clinical recovery from arthritis of hips followed resumption of specific vaccine.

matic fever seen in patients with brucellosis the problem may be simplified by finding low or normal sedimentation rates, positive tests for brucellosis and clinical response to Brucella vaccine, with serologic confirmation of the response, or response to one of the sulfonamides. When the sedimentation rate is high, as it may be in some acute joint manifestations of brucellosis, and especially when the tests for brucellosis are equivocal, the distinction from rheumatic fever is more difficult. Of course, the patient with chronic brucellosis may also develop true rheumatic fever. When, in addition, there is a mitral valve lesion with evidence of endocarditis, the differential diagnosis between brucellosis and rheumatic fever is impossible unless blood culture is positive for Brucella or for streptococci. Positive blood culture during life and the finding of vegetative endocarditis at autopsy, with positive Brucella cultures from the endocardial lesions, have been reported repeatedly. In the absence of complicating subacute bacterial endocarditis with positive blood culture there are, of course, no definitive tests for rheumatic fever.

Osteomyelitis: Figures 8 to 10 show extensive Brucella osteomyelitis in one patient. I will take only time enough to point out that this young woman suffered from exacerbations of a spreading osteomye-

Fig. 8

Fig. 8, 9 and 10. Brucella osteomyelitis of femurs in young woman, onset 1924 at age 11. Regression following institution of vaccine therapy in 1935; clinical recovery. Fig. 8 in 1930; Fig. 9 in 1935; Fig. 10 in 1940.

Fig. 9

Fig. 10

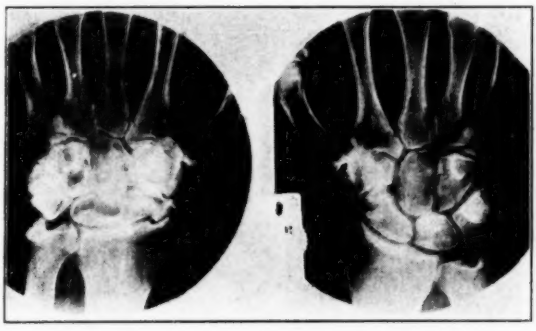

Fig. 11. Degenerative changes in carpal bones of right hand following slight trauma. Partial response to treatment with vaccine following establishment of diagnosis one year later.

litis of both femurs from 1924 until 1935 before the nature of the infection dawned upon me while studying a peculiar illness from which she was then suffering. That acute illness resolved itself into an atypical salpingitis accompanying general manifestations of brucellosis. In the eleven years between 1924 and 1935 she had had three operations on the femurs. On looking back over the reports it was found that organisms having typical morphologic and cultural characteristics of Brucella had been recovered at two of the operations (1924 and 1929) but had not been recognized because the behavior of Brucella abortus was not then widely known. The improvement shown since vaccine therapy was begun in 1935 is evident. She is now quite well clinically, is married and has had a child. However, whenever vaccine is discontinued for more than a few weeks there are evidences of clinical and serological relapse.

Neurosis: Neurosis is probably the most frequent erroneous diagnosis made in chronic, afebrile brucellosis or in patients with low-grade fever and complaints of fatigue, weight loss, joint and muscle pains, headache, mental confusion, backache, and the like. These patients may go the rounds of physicians and cultists over a period of years before someone recognizes the syndrome and carries out the tests, or stumbles upon the diagnosis through routine use of the tests. Often attention is called to the correct diagnosis only if the patient develops obvious objective symptoms or an acute febrile illness. Admittedly the differential diagnosis is difficult for brucellosis may produce a perfect textbook picture of neurosis, as pointed out by Evans after bitter personal experi-

Fig. 12. Peri-arthritis and bursitis of shoulder following slight strain; exquisitely tender and painful for six months before vaccine therapy; complete recovery in four weeks.

ence. Errors in both directions are bound to occur but they can be kept to a minimum by careful study.

Involvement of Central Nervous System: Neurobrucellosis is perhaps a good term for involvement of the central nervous system, which is not nearly as rare as is generally believed. Many reports have reached the literature but the diagnostic evidence is often meager unless Brucella can be recovered from blood or spinal fluid or from tissues at autopsy. The death rate in brucellosis is low; therefore autopsy material is not plentiful. The pathologic findings may not be helpful in differential diagnosis. While there is no characteristic picture that may be entirely relied upon, there is a growing literature tending to show that the histopathology of Brucella involvement of the brain and its coverings, while often resembling tuberculosis, especially in its tendency to nodule formation, is at least suggestive. Such a case was under my observation on my wards at the Brooklyn Naval Hospital more than a year ago. An enlisted man of twenty-four had such vague complaints of fatigue, epigastric discomfort and other symptoms suggesting ulcer, frequency and burning of urination, leg pains and cough, as to lead various medical officers to ascribe all of his symptoms to neurosis, since physical examination was essentially negative. Recurrent attacks of iritis

constituted the only objective finding, occurring several times yearly for the previous five years according to his history. Tests were positive for brucellosis but he failed to respond in the usual favorable way to Brucella vaccine. Artificial fever therapy was being considered but events subsequent to Pearl Harbor resulted in my transfer and in his survey out of the service, with a diagnosis of brucellosis. His subsequent history was given me by members of the staff of the University of Kansas Hospital. Within a month of his return to civilian life he had begun complaining of severe headaches and nuchal stiffness, usually of short duration. Then had followed, within a few days, an attack of sharp pain in the left frontal region and, four days later, weakness of the right leg and a tendency to limp. Ten days later he had had a sudden right sided hemiplegia which failed to clear up. Aside from the hemiplegia, findings were indefinite, with a questionable degree of choking of the left optic disk, moderate increase of deep tendon reflexes on the right, positive Babinski and ankle clonus, spinal fluid pressure of 280 mm., clear spinal fluid, and a cell count of 33, mainly lymphocytes. Three weeks following the onset of the hemiplegia a burr hole was made and a ventricular cannula passed toward the left lateral ventricle. Biopsy material consisted of a reddish brown, soft, cellular, granular tissue grossly resembling rapidly malignant tumor tissue or encephalitis from a recent subcortical hemorrhage. He died the same day of respiratory paralysis. At autopsy the cerebrum showed rather poorly defined areas of softening and disintegration of the brain substance. Sections through the region of the left internal capsule showed extensive acute and chronic inflammatory reaction with well-marked cuff-like accumulations of monocytes and polymorphonuclear leukocytes in the perivascular spaces. Numerous large phagocytic mononuclear cells containing congested polymorphonuclear leukocytes were recognized in many areas. Polynuclear leukocytes were diffusely scattered through the nerve tissue in some sections. There was considerable spongy degeneration and softening in the nerve tissue associated with edema, and in some areas considerable hemorrhage. Numerous compound granular corpuscles were seen in some fields and many Nissl plump cells. The diagnosis was encephalitic encephalomalacia complicating chronic brucellosis. Unfortunately no attempt was made to recover Brucella.

DeJong and others have reported instances of central nervous sys-

tem involvement in which the diagnosis was confirmed by culture and in which there was similar histopathology.

A patient with post-encephalitic Parkinsonian syndrome, apparently due to brucellosis, had been ill for nine years with a progressive, constant gross tremor of the right arm and leg and marked swelling of the entire right upper extremity of a disabling degree. Improvement was so marked following vaccine therapy as to allow her to resume her household duties.

Illustrative Case History: The following case history illustrates a differential diagnostic problem frequently encountered: A housewife of twenty-eight complained chiefly of fatigue and loss of weight. She had been ill for nearly a year following a vague febrile illness of two weeks duration which had been diagnosed as grippe. A productive cough had continued since. She also complained of frequent attacks of right lower quadrant pain. She had been operated on three months previously and a normal appendix removed. Enlargement of regional mesenteric glands had been noted (a common finding in abdominal manifestations of brucellosis). Weight loss had aggregated 18 pounds. There had been occasional periods when she felt quite well and regained a little weight. Various joints had been involved in a subacute arthritic process, with periods of complete remission.

After study at an excellent hospital no diagnosis other than "arthritis" was made. Physical examination, all usual routine laboratory examinations, including chest and gastrointestinal x-ray, had been essentially negative. Repeated sputum examinations had been negative for tubercle bacilli. There had been noted a moderate secondary anemia of the macrocytic, hyperchromic type, with normal total white count and moderate increase in lymphocytes. There had been occasional fever of from 99.2 to 99.6 degrees. The right tube had been barely palpable and moderately tender on one occasion.

Brucellosis had not been considered nor the tests done. The multiple tests for brucellosis, tuberculin test, blood complement test for tuberculosis and culture of blood and urine for Brucella were then undertaken and the sedimentation rate redetermined. Blood agglutination test was negative, skin test with Brucella organisms was positive, the phagocytic index was low (0-0-9-16), sedimentation rates were within normal limits, blood and urine cultures were negative, blood complement test for tuberculosis showed an insignificantly low titer, and tuberculin test

was positive. There was, then, an array of positive and negative laboratory findings, none of which were definite enough to diagnose or rule out tuberculosis, brucellosis or an atypical rheumatic fever. The normal sedimentation rates furnished strong evidence against tuberculosis or rheumatic fever, however. The remaining reports were not without significance when viewed in the light of the suggestive history and the lack of definite physical findings to account for it. The positive skin test for Brucella sensitization, coupled with the low phagocytic index, the normal sedimentation rate and normal white count with relative lymphocytosis, together with the history, led to a tentative diagnosis of chronic brucellosis as the possible explanation of all her complaints.

A further clue lay in the fact that many of her previous symptoms had recurred during the skin test reaction and had then subsided. Therapeutic test doses of specific vaccine furnished the last link in the chain of evidence. The first dose was followed by a mild local, focal and general reaction; the arm was tender, slightly swollen at the site of the injection, the right wrist and left knee joints became lame and moderately swollen, pelvic pain was aggravated, the right fallopian tube was tender and palpable, malaise and fatigue were increased, temperature was elevated to 100.2 degrees, within 24 hours. On the third day, following, all signs and symptoms accompanying the exacerbation ascribable to the vaccine reaction had subsided and the patient reported feeling definitely better. Following three subsequent doses of vaccine, attended by no reactions, marked subjective and objective improvement was apparent. The phagocytic index rose sharply, 10 cells now showing marked phagocytosis, 9 moderate, 6 slight and 0 none, as compared with 0-0-9-16 prior to treatment. Within three months, under continued treatment, the patient seemed well and the phagocytic index was at a still higher level (19-5-1-0). The patient was instructed to return for check-up and repetition of the phagocytic index at monthly and then longer intervals. She failed to appear until four months later when her index was found at a lower level (5-5-7-8), suggesting the likelihood of impending relapse. Resumption of vaccine was advised but the patient asked permission to defer it because she felt well, but largely because her brother-in-law, a capable internist, had expressed the doubt that she ever had had brucellosis, ascribing her recovery to coincidence or to non-specific action of the foreign protein injections. Six weeks later the patient returned saying that most of her old symptoms had

recurred and that she would now be coöperative. The phagocytic index was very low (0-8-10-7). Response to vaccine was rapid. She was treated for four months during which time she remained well. The index rose to 21-4-0-0 and remained at a high level for the next three years, without treatment. She then developed a severe measles, following which she failed to convalesce completely, complaining of great fatigue, joint lameness and malaise. She deferred returning for further observation as she was assured that this syndrome could not also be a part of an uncured brucellosis. When she did appear several months later her index again was found to be at a low level, as so often is observed in brucellosis following depleting illnesses. She was given six doses of vaccine and has remained well for the past two and a half years.

Grippe, influenza, typhoid fever, malaria, acute abdominal conditions, atypical meningococcic cerebrospinal fever can only be mentioned as among the many other illnesses that have to be considered in the differential diagnosis of acute brucellosis. Chronic brucellosis must be differentiated from endocrine dysfunctions, neuritis of other origin and a host of other diseases and syndromes in addition to the few discussed above.

Splenomegaly is not a differential diagnostic finding of value. It is mentioned because it has been said to be pathognomonic of brucellosis. It is present in a small percentage of cases of chronic brucellosis and in a higher but variable percentage of acute infections, especially of melitensis origin.

Treatment

Treatment must be outlined rather than discussed in detail. No one method can be relied upon in all cases. Many of the methods widely discussed in the literature, particularly intravenous typhoid vaccine, have proved to be valueless in my experience and that of others.

Specific Vaccine Therapy: For treatment of chronic brucellosis, heat-killed Brucella abortus vaccine has given the best results in my hands, and, with various modifications, in the hands of others who have treated significant numbers of patients and have observed them for adequate periods of time. Foshay and O'Neil have had splendid results from a nitrous acid treated Brucella vaccine which can be used without undue reaction even in the acute illness. Huddleson's Brucellin, a filtrate of all three strains of Brucella, has had favorable reports, especially in

the treatment of recent cases, but its use is attended by deliberately induced severe reactions. Many of the favorable reports of its use have not covered sufficient periods of time to allow of its proper evaluation. The commercial vaccines made from mixed strains of Brucella are best avoided because of the greater reactions induced by the presence of melitensis or suis strains. The abortus strain produces maximal immunologic response in the presence of infection due to any of the three strains. Calder believes that the presence of the suis or melitensis strains in vaccine is likely to lessen rather than to increase resistance.

The method of use of vaccine is of paramount importance. Reactions are best avoided in the majority of patients. It is not the foreign protein or shock effect upon which the efficacy of Brucella vaccine therapy rests. Dilutions of 1:10, 1:100 and 1:1000 are used to initiate treatment in sensitive patients. Intravenous vaccine is usually efficacious in those who are refractory to the intramuscular route, especially when sensitivity to vaccine persists in spite of carefully graduated dosage. Each patient's treatment must be individualized. As with other methods in other illnesses, much of the unfavorable viewpoint toward specific vaccine therapy of brucellosis comes from the experience (or inexperience) of those who have used an ineffective vaccine or ill-advised dosage, or in poorly selected cases.

Fever Therapy: When vaccine therapy fails to bring about recovery, after thorough trial and adaptation to the patient, as it will in perhaps 10 per cent of cases, other methods may be effective. Artificial fever therapy is believed by many careful observers to be the method of choice in cases refractory to vaccine therapy. It is essential to select patients carefully, to know their possible idiosyncrasies to pre-treatment sedatives and opiates and also to know their psychologic reactions to fear-producing situations. Some patients cannot help but think of the treatment cabinet as a coffin and to react badly. The optimum fever level seems to be from 105 to 106 degrees for five hours for from three to six treatments. Good results in Brucella spondylitis and other manifestations of brucellosis are reported from the Mayo Clinic and elsewhere.

Sulfonamides: The sulfonamides are of value in terminating the acute illness but not uniformly so, nor are the patients necessarily cured. Relapse follows in a variable percentage. Clinical evidence of the value of all the sulfonamides, including sulfaguanidine, has been presented by many but in no large nor controlled series. In the chronic illness they

seem to be of less value but undoubtedly sometimes are efficacious, apparently supplementing the effect of vaccine or fever therapy. Horn has reported good results from small doses over long periods of time, along with or alternating with vaccine. My own results in chronic brucellosis have not been consistent. In the subacute joint manifestations neoprontosil (oral) gave splendid results in two patients. Naturally one hopes that a compound will be synthesized that will have more uniformly specific bacteriostatic effect in the presence of all Brucella infections.

Serum and Other Methods: Foshay's serum, of goat or horse origin, has given excellent results in bringing about prompt remission in acute cases of less than four months duration. Relapse must be watched for in these patients, however. Transfusions of immune blood also have been favorably reported on in tiding patients over the acute illness.

The value of intravenous arsenicals such as neoarsphenamine is open to question. Wainwright is enthusiastic about it, as was Forest, but until recently it was uniformly unsuccessful in all of the various manifestations of brucellosis in which I employed it. Among them were two patients under treatment for syphilis, also suffering from brucellosis. They had the usual courses of neoarsphenamine and bismuth but showed no improvement in the co-existing Brucella infection until, months later, vaccine was also employed. However, one patient with a history of long-standing choroiditis, presumably a part of her Brucella infection, failed to improve under vaccine or artificial fever therapy but did respond surprisingly well to intravenous mapharsen.

In evaluating results of treatment it must be remembered that there is no absolute criterion of cure. Maintenance of a high level of phagocytic activity for many years is of utmost importance. Results must be couched in terms of "recovery," or at most, "apparent cure." The illness is prone to relapse, spontaneously or after intercurrent illness over an indefinite number of years unless carefully guarded against. It is by no means a self-limiting illness as so many of the standard texts still state; no more than is tuberculosis.

In concluding I would like to thank you for bearing with me in this rambling and incomplete discourse, and to take the opportunity to reëmphasize several points:

1. The diagnosis of brucellosis depends upon the intelligent use of the four recognized laboratory methods, with correlation of them with

the clinical findings.

2. Negative tests, individually or in aggregate, may not be relied upon to rule out brucellosis. Positive culture has been found in the presence of negative agglutination test and negative skin test and regardless of the opsonic index.

3. Positive tests must be evaluated carefully, except for positive culture which is definitive. A positive skin test alone is not proof of the existence of active brucellosis.

4. When properly arrived at, the diagnosis of brucellosis rests on firmer ground than that of many other illnesses, notably rheumatic fever.

5. The first essential to diagnosis is the willingness of the physician to admit the possible existence of brucellosis.

6. The diagnosis of brucellosis must be considered in all obscure illnesses, acute or chronic.

7. The differential diagnosis must include differentiation from innumerable diseases and syndromes ordinarily not thought of as simulated by brucellosis.

8. Known methods of treatment are satisfactory in a large percentage of cases.

CLINICAL RESEARCH ABSTRACTS*

*Studies on the Etiology of the Renal Shutdown Following Crush Injuries***

R. J. BING

Bywaters has indicated that renal failure following crushing injuries may be caused by the excretion of metmyoglobin in the presence of acidosis. The present study deals with the effect of metmyoglobin on the renal function of the acidified dog and with a comparison of its action with that of hemoglobin and methemoglobin in the normal and acidotic unanesthetized animal. Creatinine or mannitol clearances were used to measure glomerular filtration rate, paraminohippuric acid clearances for the determination of the effective renal plasma flow. Glucose Tm was determined in order to obtain information on the reabsorptive tubular capacity. Acidosis was produced by oral administration of from 80 to 100 gr. of ammonium chloride.

The infusion of metmyoglobin in five instances or of crystalline hemoglobin and hemolyzed blood in seven cases had no effect on the renal clearances of the acidotic animal. Hemoglobin infusions into three normal animals were equally ineffective. The infusion of from 4 to 12 gr. of crystalline methemoglobin into 12 acidotic dogs produced a progressive fall in clearances and in the urine flow and an increase in the blood urea during the four days following the infusion. The renal lesions consisted of hydropic tubular degeneration and necrosis, accompanied in some instances by cast formation. Methemoglobin infusions into animals with normal alkali reserve or oral administration of ammonium chloride alone resulted in no change of renal function.

* * *

The Relationship Between Blood Concentration and Blood Volume in Cardiac Decompensation

JOSEPH R. DIPALMA and PHILIP E. KENDALL

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Evidence of a conclusive nature has been presented by Gibson and Evans[1] that recovery from cardiac decompensation is always attended by a fall in blood volume as measured by a dye method (Evans blue). On the other hand, Stewart[2] has shown that during the period of recovery from cardiac decompensation there is a fall in the specific gravity of the plasma. Since it is now generally accepted that a fall in specific gravity of the plasma indicates hemodilution (or vice versa) the results of these two groups of investigations would appear to be divergent. This paper is an attempt to elucidate this problem by measuring both blood volume and plasma specific gravity in the same patient during the recovery period from decompensation.

The results obtained in a group of 24 cardiacs show that when recovery from decompensation is prompt, as evidenced by falling venous pressures and diminished cir-

* These are abstracts of presentations before the Clinical Research meeting held May 27, 1943, at The New York Academy of Medicine. This meeting was arranged by the Committee on Medical Education of the Academy.

** From the Department of Physiology, New York University, College of Medicine, aided by a grant from the Josiah Macy Jr. Foundation.

culation times, there is not only a fall in total blood volume but also a fall in plasma specific gravity. This fall in specific gravity of the plasma occurs only during the first portion of the recovery period and later returns to control values. There is also a fall in hematocrit values during this period. In cardiacs who recover very slowly from decompensation or in whom there is little diminution in blood volume these changes in blood concentration were not noted.

No explanation is apparent in this investigation for the paradoxical hemodilution of the blood during a period when the blood volume is actually diminishing. However, the results portray the advantageous physiological mechanism which exists in those cardiacs who do recover from decompensation. For during the period of recovery not only is there less blood to circulate, but it is also lighter in weight. Moreover, these findings suggest that more caution be used in interpreting blood specific gravity changes in conditions where rapid circulatory adjustments take place, as for example the shock syndrome.

[1] Gibson, J. G. and Evans, W. A. S. *J. Clin. Investigation*, 1937, *16*:833.
[2] Stewart, H. S. *J. Clin. Investigation*, 1941, *20*:1.

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A New Method for the Subcutaneous Administration of Heparin

LEO LOEWE and PHILIP ROSENBLATT

From the Department of Laboratories, Jewish Hospital, Brooklyn, New York

In reporting on a new method of administering heparin originally devised for animals,[1,2] it was stated that the method was being adapted for humans. With the coöperation of the Roche-Organon Company, a menstruum was developed for effecting slow and equable heparinization by the subcutaneous route.

This method was applied to humans with gratifying results. It has made possible and practicable the use of safe anticoagulant therapy over protracted periods. Nine cases of phlebothrombosis and thrombophlebitis and one case of subacute bacterial endocarditis have been satisfactorily treated for as long as two to seven weeks. Continuous heparinization by the cumbersome venoclysis method for more than two weeks is virtually impossible of accomplishment. The more extensive use of heparin should be encouraged by the development of this simple, effective, and more economical means for its administration.

It is important that heparin be made more available at the present time because of its application in war surgery, in the field of blood vessel surgery, and for the prevention of postoperative thrombosis and embolization. It is felt that this method of depositing heparin subcutaneously, or some further modification of it, will encourage the more widespread and rational use of this valuable anticoagulant.

[1] Loewe, L., Rosenblatt, P. and Lederer, M. *Proc. Soc. Exper. Biol. & Med.*, 1942, *50*:53.
[2] Loewe, L. and Rosenblatt, P. *Am. J. Path., in press.*

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Modification in Surgical Treatment of Herniated Nucleus Pulposus

LEO M. DAVIDOFF

In view of the desirability of producing fusion of the spine after the removal of herniated disc in many cases, a simple method for carrying out fusion has been devised, utilizing the spinous process of one of the vertebrae which is fashioned into a wedge, shaped like a double clothespin and inserted between the stumps of the spinous processes of the vertebra above and below the space where the disc occurs. In addition to the wedge, fragmented pieces of the other spinous process are used to fill the remainder of the space.

The Concentration of Vitamin A in the Blood Plasma During Pregnancy

J. M. Lewis, O. Bodansky, and M. C. Lilienfeld
Beth Israel Hospital

Plasma vitamin A and carotene determinations were carried out in 120 women at various stages of pregnancy. In twelve of these, the blood plasma was analyzed some time during the first two trimesters and again in the ninth month. The subjects were advised to eat their usual diet and a record of their dietary intake, especially with regard to vitamin A-containing foods was kept. No carotene or vitamin A concentrates were added to the diet.

The results of this study indicated that the level of vitamin A in the plasma decreases during the third trimester of pregnancy. Thus, the mean value of the vitamin A concentration in 70 women who were 6 months pregnant or less was 105.4 international units per 100 cc. of plasma (standard deviation 23.2) whereas the mean value of the determination for the 62 women in the last trimester was 91.1 international units of vitamin A (standard deviation 26.2). The difference between the mean value for the first trimesters 105.4 I.U., and that for the third trimester, 91.1 I.U., is 14.3 I.U., which is more than 3 times the standard error of the difference between the two means and hence is statistically significant.

That the level of vitamin A in the plasma decreases during pregnancy is also evident from a study of individual subjects. The plasma concentration of vitamin A was determined sometime during the first 6 months of pregnancy and again during the ninth month in each of 12 subjects. Nine of these women exhibited a drop in the plasma vitamin A concentration during pregnancy, the decreases ranging from 8 to 88 international units and averaging 37 international units. The concentration of carotene in the blood plasma does not fall during pregnancy. This may be due to the fact that only small amounts of carotene pass from the maternal to the fetal circulation.

The decrease in plasma vitamin A during the last three months of pregnancy is probably due to storage in the fetal liver as well as to utilization of vitamin A by the fetal tissues. Studies are now in progress to determine whether the addition of a vitamin A concentrate to the diet of pregnant women will prevent a fall in the vitamin A blood levels during the last three months of pregnancy.

* * *

*Acute Infectious Lymphocytosis**

Carl H. Smith

In 1941, I reported two cases of acute infectious lymphocytosis[1] in young children who, with a minimum of clinical signs and symptoms, showed an unexpected and exaggerated lymphocytosis with maximum leukocyte counts of 44,300 and 98,000 per c. mm., respectively. During March, 1943, within a period of 3 weeks, several cases of the same condition were observed at the New York Hospital. Studies made among the members of this group lend further support to the view expressed previously[1] that this condition is a specific entity possessing infectious and communicable aspects.

A child, M.S., 5 years of age, was admitted to the hospital on March 3, 1943, because of abdominal pain. The blood count showed 55,400 white cells per c. mm. with 72 per cent lymphocytes. On March 15, two other children in this family, and on March 22, K. C., a hospital contact, showed a similar blood picture. In all of the affected children the leukocytosis and lymphocytosis persisted for approximately 3 weeks. The lym-

phocytes were of the normal, small, and intermediate variety. The heterophile test was negative in the four patients. Sternal aspiration in M.S. and K.C. showed an increased lymphocytic percentage. The course in each was benign and the spleen and lymph nodes were not enlarged. A lymph node was removed for biopsy from M.S. and from K.C., and in each a strikingly similar picture was noted, consisting of obliteration of the lymph follicles with marked proliferation of the reticuloendothelium of the sinuses. Serological studies for lymphocytic choriomeningitis, influenza A and B, were negative.

Acute infectious lymphocytosis can be differentiated clinically, hematologically, and serologically from infectious mononucleosis, leukemia, and miscellaneous infections associated with lymphocytosis. It probably represents a heretofore unrecognized communicable disease in which the blood picture serves as an expression of the infection.

* From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

[1] Smith, C. H. *Am. J. Dis. Child.*, 1941, *42*:231.

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Neuro-Hormonal Regulation of Water Balance: Studies in Patients with Diabetes Insipidus

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Water, sodium, and chloride balances were studied in four patients with proved diabetes insipidus under a variety of standardized conditions.

The primary role of the polyuria of diabetes insipidus was demonstrated by water restriction and salt loading tests. The total urinary output was decreased or increased at will by the administration of diets low or high in salt, respectively. Inulin clearance revealed a normal type of variation in glomerular filtration in response to varying amounts and concentrations of salt. Improved elimination of salt and contraction of urinary volume to normal was readily accomplished by the use of posterior pituitary extracts.

Alpha-estradiol dipropionate in 10 mg. doses daily produced a positive chloride balance equivalent to as much as 3.5 gm. of sodium chloride daily in one instance, with a concomitant contraction of urinary volume, no appreciable change in specific gravity or concentration of chloride in the urine, and a normal glomerular filtration.

Desoxycorticosterone acetate in 10 and 20 mg. doses daily for five days caused at first a marked retention of sodium with decreased urinary volume and chloride concentration. In the "release" phase a negative sodium balance and an increased urinary output and concentration of chloride resulted.

Amidopyrine decreased the polyuria with a simultaneous increase in the urinary specific gravity and concentration of chloride. No effort was made to determine the nature of this effect.

* * *

Test of Viability of the Gut in Local Obstructions

JOHN HERRLIN and S. T. GLASSER

The problem of determining the viability of intestine not infrequently presents itself in cases of obstruction. In these instances, surgical judgment implies a difficult decision even in the best of hands. One must choose between a simple release of the obstruction,

and resection with anastomosis. The mortality in the latter is obviously increased. Since the pathology observed is usually dependent upon vascular changes, we are confronted with a situation analogous to one seen in cases of peripheral vascular disease, namely, reflex or axone—reflex spasm of the collateral circulation. We have based our test which is also of therapeutic value, on this principle. A perivascular injection of novocain into the mesentery of the involved segment often results in a prompt restitution (one to two minutes) of the intestine. In some instances the novocain injection placed at the mesenteric border of the gut proves more satisfactory. Further experiments are being conducted at the New York Medical College towards a better understanding of the mechanism involved.

* * *

A New Experimental Laboratory Animal, the South African Clawed Frog (XENOPUS LAEVIS): *Its Use in Pregnancy Diagnosis, Hormone Assays, and Endocrine Evaluations*

ABNER I. WEISMAN and CHRISTOPHER W. COATES
Jewish Memorial Hospital and New York Zoological Society

Xenopus laevis Daudin, the South African clawed frog, is established as a new, satisfactory, and versatile laboratory animal. The use of the animal is predicated on the response—extrusion of eggs—to hormone stimulation. Its chief present value is its remarkable accuracy in the early diagnosis of pregnancy; the speed with which the diagnosis may be made, and the ease with which the diagnosis may be read; 641 cases are reported with 99 per cent accuracy. No false positives are recorded. Reports on gonadotropic hormone assays indicate that true anterior pituitary extracts are more potent than either of the gonadotropes obtained from pregnancy urine or serum.

Tubal pregnancy diagnosis was confirmed in 9 cases.

In clinical endocrinology, neither climacteric nor post-climacteric urines gave positive results, but urine from cases of hydatid mole gives positive results in extremely small dosages.

Further studies are being made in glandular neoplasms.

* * *

The Complement-Fixation Test for Lymphogranuloma Venereum: Results Obtained With Its Use

ARTHUR W. GRACE
From the Long Island College Hospital and the Department of Dermatology and Syphilology Long Island College of Medicine

A number of complement fixation tests for lymphogranuloma venereum were uncertain and unsatisfactory owing to the low concentration of virus in the antigens. The growth of the virus in the yolk sac of the developing chick has enabled suspensions of the virus to be obtained which are practically free from inert material. Antigens of any desired concentration of virus can, therefore, be prepared which are both sensitive and specific. By their use it has been shown that about 50 per cent of persons with gonorrhea or acquired syphilis have, in addition, asymptomatic lymphogranuloma venereum. Examination of the sera of children with congenital syphilis has proved that there is no cross fixation between the reagins of syphilis and those of lympho-

granuloma venereum. Agreement between the results obtained with the Frei intradermal test and the complement fixation test has been found in 85 per cent of a group of 200 normal and lymphogranulomatous people. The bulk of the remaining persons had a positive complement fixation reaction and either showed clinical manifestations which could be regarded as lymphogranulomatous or had other venereal diseases. It is, accordingly, felt that the complement fixation test is a more sensitive procedure for the diagnosis of lymphogranuloma venereum than is the Frei cutaneous test. There is a definite relation between the average size of the Frei reaction and the average level of the complement fixing titre of the sera of lymphogranulomatous persons; the larger the reaction, the higher the titre. It was also found that the average titre of sera of cases of proctitis with stricture was 6 to 7 times greater than that of persons in whom the lymphogranulomatous infection was, and had always been, asymptomatic.

* * *

The Role of the Lymphatics In Ascending Urinary Infections

JOHN L. ALLEY*

A discussion of the anatomy of the lymphatic system of the genitals in its relationship to the urinary apparatus. The possibility of extension of infection to the kidney from below is admitted, but the precise route is subject to controversy. Efforts were made to inject the lymphatics in rabbits and guinea pigs with India ink. The ink was sterilized, diluted with an equal amount of normal saline, and injections were made into the corpora of the penis. Multiple injections at varying intervals were made. Careful examination of the tissues of autopsied pigs were then made and sketches accompany the presentation.

CONCLUSIONS: Infections apparently may spread upward in the genito-urinary system. The burden of drainage from the lower organs is borne by the lumbar lymphatics. On reaching the level of the kidneys, infection may go on past to empty into the blood stream and thence to the kidney, or it may reverse the normal lymphatic flow at this level to invade the kidney by way of the perivascular lymphatics.

* Graduate Fellow in Surgery, New York Medical College, Flower and Fifth Avenue Hospitals; under the direction of Joseph H. Fobes, Department of Graduate Surgery, New York Medical College, and Professor J. A. Hyams, Post-Graduate Hospital.

* * *

*Certain New Considerations In Local Sulfonamide Therapy**

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Controlled observations have shown that the local use of sulfonamides has not scored the brilliant results that follow their use in systemic infections. It is the purpose of this paper to describe the results of studies of infected wounds in man that have revealed certain heretofore unrecognized factors that may lead the way to successful local sulfonamide therapy of infected wounds.

From the experimental observations as shown in charts, diagrams, and in color photographs these new considerations of local sulfonamide therapy may be summarized:

(1) Present techniques of application *maintain* but slight if any concentration of drug in the infected wound. Absence of drug coincides with failure to control infection.

(2) Infected wounds develop very low

hydrogen ion concentrations: pH of 5.0 to 5.5 is frequently measured in the exudates.

(3) The lowered hydrogen ion concentration reduces the activity of sulfanilamide 10 to 100 times so that practically unattainable concentrations are required for bacteriostasis in the acidic exudates.

(4) Sulfadiazine and sulfathiazole (which are many times more potent than sulfanilamide) are not greatly "inactivated" by the lowered pH but they are rendered insoluble. This prevents their dissolving in wound fluids and exudates, a prerequisite for control of infection. Use of their highly soluble sodium salts overcomes this major obstacle and produces bacteriostasis without irritation to tissues or delay in the growth of epithelium.

(5) Persistent failure to detect sulfonamide "inhibitors" in numerous samples of pus (obtained without novocaine) suggests that failures with local sulfonamide therapy may be the result of the four previous factors and not because of the presence of various types of "inhibitors."

* This work was done under a contract between the Office of Scientific Research and Development and Columbia University.

* * *

Nutritional Deficiency In the Etiology of Menorrhagia, Metrorrhagia, Cystic Mastitis and Premenstrual Tension: Treatment With Vitamin B Complex

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GERSON R. BISKIND

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In previous experiments in the rat, it has been found that the liver loses its ability to inactivate estrogen in vitamin B complex deficiency and that this function can be restored by the addition of brewers' yeast to the diet. In contrast, the inactivation of androgen was found not to be significantly impaired in vitamin B deficiency. Failure to inactivate estrogen while androgen continues to be inactivated leads to a serious alteration in the estrogen-androgen equilibrium. On the basis of these animal experiments an investigation was made to determine whether there is any clinical correlation between nutritional deficiency and the occurrence of syndromes related to an excess of estrogen, in particular, menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension. A striking correlation was found and therapy of these conditions with vitamin B complex was therefore attempted. Prompt and often dramatic improvement occurred with vitamin B complex orally or orally and parenterally. Oral lesions of nutritional deficiency in patients with the syndromes associated with an excess of estrogen, and the changes under treatment, are illustrated in Kodachrome.

Titration and Neutralization of the Western Strain of Equine Encephalomyelitis Virus In Tissue Culture

C. H. HUANG

From the Departments of Medicine and Bacteriology, College of Physicians and Surgeons Columbia University

Instead of injecting the virus or serum-virus mixtures into animals, one drop of the material from each dilution was inoculated into tissue cultures. After 48 hours of incubation, pieces of tissue from each culture were transferred and patched with plasma in Carrel dishes. They were incubated and readings were made under low power microscope 48 hours later.

It was found that cells which were not infected or had overcome the infection, grew out in the plasma patch. Contrariwise, when virus was present, no growth from the explant was observed.

The method hereby presented has several advantages, namely: reduction of cost of experiments since one chick embryo can be used for a complete titration experiment; removal of the variable of individual animal reactivity; and the tissue culture may be a more sensitive method for the detection of the virus and neutralizing antibodies. It was found that the neutralization obtained in tissue culture is 100 to 1,000 times greater than that observed in the intracerebral mouse test.

Recently, a more simplified method has been developed with promising result. This was based on the difference in the change of the pH of the medium in infected and non-infected tissue.

* * *

The Effect of Sodium Thiosulphate on the Blood

LINN J. BOYD, LOUIS GREENWALD and JOSEPH LITWINS

Department of Medicine, Flower and Fifth Avenue Hospitals

For more than a decade this chemical has been advised for the prevention of post-operative thrombosis and other disturbances of clotting. Adequate examinations of its effect on the blood have never been conducted. In vitro and in vivo experiments have been performed by the writers on more than two hundred patients during the past year. The influence of the chemical on blood morphology, chemistry and clotting was examined. Studies were also conducted on more than one hundred patients before and after operation.

Sodium thiosulphate does influence clotting, but the solutions must be much more concentrated and the doses much larger than those employed by most clinicians. None of the untoward effects associated with heparin and dicoumarin are observed. The chemical is practically devoid of toxic effects. Observations were also made on the question of single and multiple injections.

No changes in the blood morphology occurred when enormous doses were given and the patients followed for months. There are also no significant changes in blood chemistry. There is a variable latent period before the effect appears which bears very definitely on its therapeutic application. A possible mode of action is suggested.

*A Rapid Pregnancy Test (Two to Six Hours)**

U. J. SALMON, S. H. GEIST, C. S. POOLE and A. A. SALMON, B.S.

The test is based on the observation that following the injection of pregnancy urine into immature female rats a vasodilatation of the ovarian vessels occurs as early as two hours after the injection. This reaction is visible to the naked eye—the ovaries being engorged, bright red in appearance and enlarged in contrast to control ovaries which are pale pink in color. In approximately 5 per cent of rats the vasodilatation is only slight at 2 hours and becomes maximal between 3 and 6 hours after the injection; 2 cc. of urine is injected under the dorsal skin of each of four immature albino rats, weight 35-45 grams. Two animals are autopsied at the end of two hours and if the results are negative or questionable the remaining two animals are autopsied four hours later. The accuracy of this reaction as a test for pregnancy was determined in a series of over seven hundred unknown specimens of urine comprising normal pregnancies, incomplete abortions, ectopic pregnancies, hydatidiform mole, chorioepithelioma, functional amenorrhea, menopause (natural, surgical and radiotherapy), uterine fibroids, menorrhagia, metrorrhagia and functional dysmenorrhea. The accuracy of readings at 2, 4 and 6 hours were compared. Readings of the control urine specimens from normal non-pregnant women were 100 per cent accurate. Correct positive readings were made in 96.3 per cent of the pregnancy cases at 2 hours; in 97.2 per cent at 4 hours and in 98 per cent of the cases at 6 hours.

This test has the practical advantages of rapidity, simplicity of reading, inexpensiveness and ease of obtaining the test animals. The latter two are particularly important at present because of the growing scarcity and increasing cost of rabbits.

* This research was carried on at the Mount Sinai Hospital.

* * *

Nitrogen Retention, Creatinuria, and Other Effects of the Treatment of Simmonds' Disease With Methyl Testosterone

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RANDOLPH WEST
Associate Physician, Presbyterian Hospital

The use of methyl testosterone orally has produced striking clinical improvement with accompanying laboratory changes in 4 cases of marked anterior pituitary insufficiency or Simmonds' disease. The diagnosis was confirmed in one case by the complete lack of demonstrable pituitary cells at autopsy on gross and microscopic examination. Seborrhea failed to appear despite the restoration of other secondary sex characters, suggesting that androgens normally act to produce seborrhea only after the skin has been prepared by some basic mechanism or mechanisms, which are wanting in hypophyseal failure. From the laboratory standpoint, methyl testosterone was found to cause nitrogen retention and persistent weight gain in the absence of hypophyseal function. A marked increase in creatinuria was also noted during the period of methyl testosterone therapy.

The use of methyl testosterone is suggested as an effective therapeutic agent in anterior pituitary insufficiency or Simmonds' disease.

The Physiopathological Aspect of Muscles in Infantile Paralysis

JOSEPH MOLDAVER

In this presentation an attempt has been made to discuss the chief disorders resulting from infantile paralysis. The affinity of the virus for the anterior horn cells of the spinal cord is striking. Lesions are also found in the posterior horn cells and dorsal root ganglia. In addition, other parts of the central nervous system may be affected. The paralysis is a flaccid one. The affected muscles become atrophic and toneless; the tendon reflexes and some cutaneous reflexes are absent. In the paralytic or paretic muscles, neuromuscular degeneration can be evidenced by chronaxie measurements. The degree of the injury of the anterior horn cells is evaluated by this test; the greater the lesion, the higher is the chronaxie. This helps the diagnosis and also the prognosis. Muscles with total neuromuscular degeneration (completely denervated) are doomed. Muscles with partial neuromuscular degeneration (partially denervated) may recover partially or even completely. Inflammation of the sensory protoneurone is not necessarily found at exactly the same level as the injury of the anterior horn cells; therefore, pain and tenderness of the muscles may be found in non-paralyzed as well as in affected muscles. Pain is a referred pain, increased by stretching of the muscles. Clinically speaking, most of the lesions of the sensory protoneurones clear up completely; sensory disturbances are not frequently seen in the chronic stage.

A new concept was recently described by Kenny. This concept is fundamentally different from the one accepted for more than a century. According to this concept, infantile paralysis is a "spastic" not a flaccid paralysis. The muscles affected by the disease are those in so-called "spasm," "the most damaging symptom." The danger of paralysis lies mainly in allowing "spasm" to continue. The muscles opposed to those in "spasm" become "mentally alienated," divorced from the patient's mind. "Alienated muscles appear toneless and incapable of voluntary contraction but are never painful or tender indicating that they are not the muscles involved directly by the disease." "Even the tendon reflex of such muscles disappears; alienated muscles become permanently paralyzed and atrophied if steps are not taken early to restore such muscles to action." The third and least important symtom described is "incoordination;" according to the concept, it is due to a "disorganization of the regulating centers."

The various parts of the Kenny concept were investigated by means of chronaxie and action potential studies in forty-nine patients. Muscles called "alienated," muscles in "spasm" as well as normal muscles were explored. The following were found:

A. "Spasm" is not a separate entity but a complex phenomenon. It is the result of: 1) meningeal irritation of the posterior roots, 2) lesions of the dorsal root ganglia, and 3) increase of the normal tonus in healthy muscles opposed to weak or paralyzed muscles.

Muscles in marked "spasm" generally showed normal chronaxie, that is to say they were without any trace of neuromuscular degeneration. The meningeal component of the so-called "spasm" disappears relatively quickly. Irritation of the dorsal root ganglia lasts longer than meningeal reaction. The last and most persistent type of "spasm" is the one due to the increase of the normal tonus in strong muscles. This has nothing in common with true spasm.

B. A paralytic or paretic muscle called "alienated" is always to some degree in neuromuscular degeneration; this is the result of damage to the anterior horn cells. Depending upon the intensity and extent of the lesions, degeneration is more or less marked. It will be indicated by chronaxie measurements. Among the muscles called "alienated," some were in partial and others were found in total neuromuscular degeneration.

C. If among the muscles which have to carry out motion, one or several are paralyzed or paretic, there is necessarily a dis-

turbance in the function of the extremity involved. The automatic regulation of the movement will be interfered with as well as the voluntary movement.

CONCLUSION:

The findings reported here show that the Kenny concept of infantile paralysis can not be accepted.

The so-called "spasm" is not the "most damaging symptom" of the disease. There is no functional paralysis nor a "physiological block" in the paralytic or paretic muscles. These muscles are not "erased" from the patient's mind but are damaged by anterior horn cell lesions. Moreover there is no clinical evidence of a disorganization of the regulating centers leading to "incoordination."

* * *

*Traumatic Shock**

MAGNUS I. GREGERSEN

Professor of Physiology, College of Physicians and Surgeons, Columbia University

The present report constitutes a brief statement of the more important conclusions that my collaborators and I have reached during the past year and a half from our studies on experimental and clinical shock.

Blood pressure is not a reliable index of the severity of injury nor of the degree of shock.

Reduction in blood volume is the initial and determining factor in the train of events preceding shock from hemorrhage or trauma. In both dog and man a reduction of more than 35 per cent leads to shock. Generally speaking a patient in severe shock has lost about two quarts of blood.

Contrary to the view which has been widely proclaimed, hemoconcentration is not a criterion of shock, and the gradual failure of the circulation and appearance of symtoms cannot be ascribed to a progressive decrease in blood volume. The reduction in volume occurs at the time of injury. Thereafter not only the blood volume but the hematocrit and plasma protein level remain essentially unchanged. Accurate measurements of the changes in volume of the traumatized limbs (dogs) show that the "local fluid loss" equals or exceeds the loss in blood volume. These facts together with other experimental evidence disprove the theory of general increase in capillary permeability. Capillary leakage is limited to the injured region. Elsewhere fluid is absorbed from and not lost into the tissues.

Gradual failure of the circulation after hemorrhage or trauma is related to a progressive decrease in cardiac output (Fick method) which may fall to 10 per cent of the normal, to reduction in oxygen consumption (50 per cent of normal), and to increased A-V oxygen difference (from normal of 4 vols. per cent to 15-20). Complete analyses of the blood have revealed extreme changes in arterial CO_2, pCO_2, pH, lactate, phosphate, and pyruvate. The serum potassium remains unchanged until the terminal stages are reached. During the last hour before death it may rise to two or three times the normal level. The alterations in the blood are characteristic of the metabolic disturbances produced by severe anoxia. They are not peculiar to traumatic shock.

* This work was done partly under grants from the Josiah Macy, Jr. Foundation and partly under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University.

Study of the Circulation in Clinical Shock

A. COURNAND, R. L. RILEY, E. S. BREED and D. W. RICHARDS, JR.

Measurements of the circulation have been carried out in 46 cases of injury of various types and in varying degrees of shock, including 25 cases of severe skeletal trauma, 3 cases of chest injury, 8 cases of hemorrhage, 4 cases of burn, and 6 cases of abdominal injury.

Basic measurements employed included: (a) plasma and blood volumes, (b) arterial pressure (Hamilton manometer), (c) peripheral and central (right auricle) venous pressures, (d) cardiac output (direct Fick technique), (e) arterial and mixed venous blood gases, pH, lactic acid, (f) pulmonary ventilation and respiratory gas exchange, (g) renal clearances. The pressures in the right auricle and mixed venous blood samples were obtained by passing a catheter directly into the right heart.

The description derived from the data obtained conformed to the accepted view that established shock in the various types of injury studied, was due to a rapid and precipitate failure of the circulation, usually associated with inadequate return of blood flow to the heart. The chief findings were decreased cardiac output, low pressure in the right auricle, low arterial pressure, and decrease in blood volume. With one exception all cases of shock due to skeletal trauma showed hemodilution. Burns and abdominal injuries showed hemoconcentration.

In many cases the effects of blood transfusion and in a few cases the effects of adrenal cortical extract or rapid saline infusion upon the circulation were followed by repeated measurements.

Two individual cases, one of hemorrhage, and one of skeletal trauma (fractured pelvis), are described.

* * *

Plasma Clot Suture of Peripheral Nerves

I. M. TARLOV

Young and Medawar have attempted to improve the accepted method of uniting nerves with silk by the use of clots prepared from cockerel plasma and chick embryo extract. The inconveniences involved in the preparation of these materials and, more particularly, the inflammatory and fibrotic reaction resulting in animals of other species, led to the introduction of the technique of autologous plasma clot suture of nerves. The development of a suitable mold in which nerves can be sutured with plasma clot made for more accurate alignment and stronger union of the nerve ends as well as for a broader field of usefulness of the method.

When nerve ends cannot be united without strain, then plasma clot suture is undesirable since the junction may subsequently come apart. Under these circumstances, following a suggestion by Lt. Col. R. Glen Spurling, tantalum wire (0.003 inches in diameter) has been employed as tension sutures to approximate the nerve ends while accurate apposition is achieved by means of plasma clot. The use of this combined technique eliminates the likelihood of separation of the sutured nerve ends and makes it possible to avoid much of the knuckling of nerve fibers and distortion at the suture site that is apt to follow the classical method of nerve suture by means of thread stitches. The results of plasma clot suture of peripheral nerves are encouraging.

The Production of a Sulfonamide Antagonist and A Sulfonamide Potentiator by the Tubercle Bacillus

WALSH MCDERMOTT and ALICE TRACY

When tubercle bacilli (H-37RV) are grown upon synthetic media, bacteria-free filtrates of the culture produce two entirely different effects when added to media containing E. coli and sulfanilamide.

In low dilutions (1-5, 1-10) the filtrates of the tubercle bacillus cultures potentiate the bacteriostatic action of sulfanilamide on E. coli grown in synthetic media.

In higher dilutions (1-50 through 1-1000) the filtrates of the tubercle bacillus cultures completely neutralize the bacteriostatic effect of 7 mg. per cent sulfanilamide on E. coli. The addition of further dilutions of the tubercle bacillus filtrates (1-5000 or more) has no effect upon the usual bacteriostasis of E. coli induced by sulfanilamide.

Two phenomena are manifested here: (1) A sulfonamide-potentiating effect which is present in higher concentrations but which disappears on dilution. (2) Sulfonamide antagonism demonstrable in certain dilutions but masked in the more concentrated dilutions by the potentiator.

The sulfonamide potentiator effect present in the higher concentrations of the filtrates can be shown to be due to the presence of a substance which becomes bacteriostatic only in the presence of sulfanilamide. In contrast to other potentiators and synergists which have been reported, these products of the tubercle bacilli (as filtrates), in the absence of sulfonamide, are stimulants to the growth of E. coli. Yet when added to sulfanilamide solutions, the bacteriostatic power of the resulting combination is considerably increased over the controls containing similar concentrations of sulfanilamide.

The antagonist has properties in common with para-aminobenzoic acid. The tubercle bacilli filtrates have a positive diazo reaction. If the diazotizable substance were para-aminobenzoic acid, it would be present in amounts averaging 0.03 mg. per 100 cc. of a 6-week culture. When a known solution of this concentration of para-aminobenzoic acid is tested parallel to the tubercle bacilli filtrate, the sulfonamide antagonism produced by both is of the same order of magnitude.

It can be shown that neither of the two phenomena observed in the action of the H-37 filtrates can be reproduced by comparable experiments with purified tuberculoprotein. Both the antagonist and potentiator are ether-soluble. The former is unaffected, the latter almost entirely removed, by acid precipitation. Boiling with sulfuric acid does not prevent either the antisulfonamide or sulfonamide-enhancing effect. It does, however, slightly increase the sulfonamide potentiator effect when the solutions contain purified or unpurified tuberculoprotein.

As far as we know, this is the first demonstration of the production of a sulfonamide potentiator by a pathogenic microörganism.

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The following abstracts were presented before the Clinical Research meeting May 27, 1943, but publication was withheld.

Vitamin D in human milk, Louis J. Polskin, Benjamin Kramer, Albert E. Sobel.

Further studies on penicillin as a chemotherapeutic agent, Martin H. Dawson, G. L. Hobby, K. Meyer, E. Chaffee.

Renal circulation in shock, Henry Lauson.

Measurement and recording of intrauterine pressure, Sergei Feitelberg, I. C. Rubin.

Probable mechanism by which somatic changes in certain emotional states are mediated, A. T. Milhorat, S. M. Small, E. J. Doty, W. E. Bartels.

Abstracts Read by Title May 27, 1943

In addition to the foregoing abstracts presented at the Clinical Research meeting held at The New York Academy of Medicine, May 27, 1943, and thereafter submitted for publication, the following manuscripts which could not be presented in the limited time available, were read by title:

1. The use of soluble sulfonamides in extensive third degree burns, Charles L. Fox, Jr., Joseph Tamerin
2. Refrigeration anesthesia and refrigeration therapy, S. Thomas Glasser
3. The diagnosis of herniation of the intervertebral disc, Thomas I. Hoen
4. Acute perforation of gastroduodenal ulcers seen at the Metropolitan Hospital from 1930 to 1941, Walter L. Mersheimer
5. Blood volume studies in man, Robert P. Noble, Magnus I. Gregersen
6. Sympathectomy in chronic ulcers and infections of the extremities, Kenneth C. Peacock
7. Local use of sulfathiazole in eye infections with special reference to epidemic kerato-conjunctivitis, Charles A. Turtz
8. Correlation of peritoneoscopic findings with clinical and pathological factors, especially of the liver, Leonard P. Wershub
9. Sulfadiazine and its sodium compound in the treatment of meningococcic meningitis and meningococcemia, Emanuel Apelbaum, Jack Nelson
10. Migraine—a new rationale of treatment, Miles Atkinson
11. Resistance of the Rhesus monkey to 90 plus per cent oxygen, Martin Friedrich, David M. Grayzell
12. The nature of the solutions in the urine of the excreted products from sulfadiazine therapy, D. R. Gilligan, Walsh McDermott
13. Laurence-Moon-Biedl syndrome, S. P. Goodhart
14. Dangerous and safe methods of oily nasal applications, Bruno L. Griesman
15. The tuberculin patch test, Maurice Grozin
16. Hypoprothrombinemia in non-jaundiced cases. The effect of oral and parenteral 2-methyl 1-1, 4-naphthohydroquinone dye phosphoric acid ester tetra sodium salt, Norman H. LeTourneau
17. Treatment of pneumococcal pneumonia with sulfadimethyldiazine, Elmer H. Loughlin, Richard Bennett, Miss Mary E. Flanagan
18. White men in the tropics, James L. McCartney
19. The bone changes in erythroblastic and other related anemias, Savas Nittis
20. The effects of the synthetic and natural hormone of the adrenal cortex on survival and melanin deposition in black rats maintained on filtrate factor deficient diets, Elaine P. Ralli, Irving Graef
21. Allergy to sulfonamides, Bret Ratner
22. Clinical observations on tissue temperatures, their therapeutic and pathological effects, James R. Lisa, F. K. Safford, Jr., M. B. Nathanson, Lymon Weeks Crossman
23. Magnesium sulphate in paroxysmal tachycardia, David Scherf
24. Electrocardiographic changes after acute loss of blood, David Scherf
25. The saline-procaine test in the differentiation of psychogenic "rheumatic" disorders, Otto Steinbrocker, Paul Kuhn

LIBRARY NOTES

DEATH OF DR. ARNOLD C. KLEBS; ACADEMY LIBRARY CONSULTANT

DR. ARNOLD C. KLEBS died on 6 March at Nyon, Switzerland, his home for many years. He had been a Consultant in Bibliography to this Library since 1929.

Dr. Klebs was born at Berne on 17 March 1870 and was the son of Dr. Edwin Klebs (1834-1913), the distinguished professor of pathology and eminent bacteriologist. (By the way, the textbook on pathology of the elder Klebs is still authoritative on very obscure conditions or lesions). Arnold Klebs was educated at Prague, at the University of Zürich, and in 1895 obtained his medical degree at Basle. Very shortly after that he came to the United States and practised in Chicago. His great interest was tuberculosis and under his editorship *Tuberculosis, a Treatise by American Authors* appeared in 1909. Dr. Klebs became a United States citizen in 1904. About the year 1909 he returned to Switzerland but made frequent trips to this country.

Fuller accounts of his life have been given, but here it is sufficient to point out his connection with this Academy as well as some of the facets of medical history and bibliography which interested him and about which he wrote. One of the first subjects which occupied his attention was inoculation against smallpox and he published a paper, "The Historic Evolution of Variolation," in the *Bulletin of the Johns Hopkins Hospital* in 1913. Heft 7 of the periodical, *Zur historischen Biologie der Krankheitserreger*, Giessen, 1914, constituted a more comprehensive account of inoculation by Klebs. Once he became interested in a subject, he never put it aside for good and all, and I warrant that to his last days he was constantly adding to his bibliography of variolation. Dr. Klebs was an authority on the anatomical work of Leonardo da Vinci and the intricacies of the publications which contain reproductions of the drawings. One paper on Leonardo came out in the

Bulletin of the Society of Medical History of Chicago, in 1916; and another in the *Boston Medical and Surgical Journal*, 1916.

One will always think of Dr. Klebs in connection with herbals. He probably knew as much as anyone about them in their printed form, and especially about their sources and their family trees. He listed the editions of that Latin poem known as the "Macer Floridus." Also he distinguished three families of editions which he termed the "Herbarius," "Gart" and "Hortus," whilst formerly the knowledge of this large group of herbals was most confused, and they were entered under almost as many as fifteen titles. To bring order out of chaos, meant that Dr. Klebs had to examine and compare scores of copies of different editions. Articles on the subject appeared in 1917 and 1918 in *Papers of the Bibliographical Society of America*, volumes 11 and 12. And under the title of "Herbal Facts and Fancies" he wrote an introduction to l'Art Ancien's *Catalogue of Early Herbals*, Lugano, 1925.

Dr. Klebs was a deep student of the earliest printed tracts on the plague; and in 1925 with Mlle E. Droz published from Paris in French and in English a little book, *Remedies against the Plague* ("Scientific Documents of the XVth Century," vol. 1), which contains facsimiles of the three earliest French tracts, a list of the fifteenth century printed texts, and valuable notes. He and Karl Sudhoff collaborated in the book, *Die Ersten Gedruckten Pestschriften*, Munich, 1926. Dr. Klebs discusses the bibliography of the incunabula; provides a list arranged alphabetically by author, as well as one by year from 1472 to 1501; tabulates the works by place of publication arranged alphabetically; and finally, treating the subject geographically, he has a long section on the history of the printing of these plague tracts.

Dr. Klebs took a wide view of the study of the history of medicine, and anyone who wishes to learn the history of this study and how it has been carried out since it began would do well to consult the article by him. Read at the meeting of the Johns Hopkins Hospital Historical Club on 8 December 1913, his address came out in the *Bulletin of the Johns Hopkins Hospital*, 1914, with the title, "The History of Medicine as a Subject of Teaching and Research." In the last letter I had from him (28 February 1942), saddened by the long illness of his wife which had become so serious almost five months before, he refers to his ambitions which had not been fulfilled: "Already the last war prevented the carrying out of my plan of returning to the United States for the Balti-

more Institute which I had pushed since 1913 and which I think would have materialized then, but became impossible then." But we know that at Baltimore his ideas have borne abundant fruit.

I think the only paper Dr. Klebs read at this Academy was before the Section of Ophthalmology in 1927. It was published in our *Bulletin* that year with the title, "Historical Perspectives in Ophthalmology."

Dr. Klebs's interest in herbals and plague tracts printed before 1501 has been referred to. But he was not content with these incunabula, and studied those of medicine and science as a whole. His *apologia* for such work may be found in his address delivered before the Bibliographical Society of America ("Gleanings from Incunabula of Science and Medicine," *Papers of the Bibliographical Society of America*, Chicago, 1932). It will be seen from the following quotation (p. 58) when, where, and how this began:

> I have given to the study of incunabula of medicine and science the better part of the past fifteen years after having been introduced to them in the Surgeon General's Library by Colonel Fielding H. Garrison. I am now engaged with the final revision of a general bibliography of the incunabula of science and medicine, a work which, with the welcome assistance of the New York Academy of Medicine, I hope to bring to an early termination. I have extracted from my records data which I believe can throw a clearer light than hitherto obtainable, on the extent, on the various aspects, and on the paths of dissemination of the earliest scientific literature as it issued from the first European presses.

Dr. Klebs identified and catalogued during 1915-16 the incunabula in the Army Medical Library. He volunteered to catalogue our collection, and in 1929 this was accomplished with the help of Miss Lesta Ford, now Mrs. A. G. Clay. The list with brief entries, prepared by Miss Ford, was published in the *Annals of Medical History* in 1930. He became the acknowledged authority upon such incunabula and his advice was sought by scholars and booksellers the world over. His library, set in the garden at Nyon, became a centre. To it incunabula arrived by ordinary or air mail to be identified or to be looked over by Dr. Klebs before they were purchased by Dr. Harvey Cushing or other friends. His books have been left to the Yale University School of Medicine Historical Library and so will join those of Dr. Cushing. Dr. Klebs was in closest touch with Mr. Victor Scholderer, the expert on

fifteenth century books at the British Museum; and in compiling the list of incunabula of the Royal College of Surgeons of England, the Librarian, Mr. W. R. Le Fanu, acknowledges the help of Dr. Klebs (*Annals of Medical History*, 1931).

In 1929 Dr. Klebs offered, if encouraged and helped by this Academy, to publish a catalogue of all the incunabula of science and medicine. We accepted with alacrity and it was agreed that the book should be the first publication in the "History of Medicine Series issued under the Auspices of the Library of The New York Academy of Medicine." Even Dr. Klebs did not foresee the difficulties of the task and the length of time it would require; and of course he did not know he would suffer from ill health. We were delighted, however, that his "Incunabula Scientifica et Medica. Short Title List" was published in *Osiris*, Bruges, 1938, vol. 4, pp. 1-359. He presented the Library Publication Fund Committee with fifty bound reprints (dated 1937) and this title appears first in our History of Medicine Series. Dr. Klebs regretted that the work was not a much fuller one, provided with discussions of the incunabula which fell into various subject classes and with elaborate notes. He also hoped to include a chart referred to in two characteristic letters extracts from which are given below, the first being written to me from Nyon, 19 June 1931:

> But joking aside, there is so much to ponder about in these new realisations of human science, that I have had to rewrite great parts of my historical introduction to the incunabula, I hope with some result. . . . I am not giving a paper at the Congress [International Congress of the History of Science and Technology, London, June 1931] but display only an enormous wall map at the Science Museum. On it I have painted in glaring colors the great domains in various chronological aspects, of that of Print and Paper, of Parchment, of Papyrus, and of wood, stone and brick. Not a suggestion of politics, all high brow spirits. It really is quite interesting. Someday we will hang it up in the rare book room. . . .

And speaking of it again in a letter to the late Dr. Linsly R. Williams (30 July 1931) he writes:

> . . . and there are other demands on me which I cannot shirk, such as attendance at the International Congress for the History of Sciences in London where I showed a large map illustrating the diffusion of scientific thought from the beginning to the 15th

century. This will be included in the work and increase its interest, I think. . . .

The "Short Title List" has proved, however, to be a tool of great use to the students of science and medicine of the fifteenth century. Arranged alphabetically under about 650 authors are over 1,000 titles and more than 3,000 editions. Place, date, and printer are given, if known definitely; and references are provided to full descriptions previously published of the incunabula. Also one is told where copies of the numerous editions may be found and consulted. At the end, cross references are given to the various names by which the authors are known.

Dr. Klebs spent many hours in the Library when he came over from Nyon to New York almost every winter, and when here he was sure to look up old friends such as Dr. George Draper and Professor Lynn Thorndike. We are grateful to him for his advice about the Rare Book and History Department. Dr. Klebs knew the true value of books and hated to be called a "bibliophile" if by that was meant one who cared more for the binding and for the rarity of a copy—especially with unopened leaves—than for its contents and its place in the development of knowledge.

ARCHIBALD MALLOCH

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Adolph, E. F. *Physiological regulations.* Lancaster, Cattell, 1943, 502 p.

American Medical Association. Special Exhibit Committee on Fractures. *Illustrated primer on fractures.* 5. ed. Chic., Amer. Med. Assoc., 1943, 119 p.

Ballenger, H. C. *A manual of otology, rhinology and laryngology.* 2. ed. Phil., Febiger [1943], 334 p.

Batten, L. W. *Health for the young.* London, Allen [1942], 176 p.

Bockus, H. L. *Gastro-enterology.* Phil., Saunders, 1943, v. 1.

Bogert, L. J. *Nutrition and physical fitness.* 4. ed. Phil., Saunders, 1943, 500 p.

Cole, W. H. & Puestow, C. B. *First aid, surgical and medical.* 2. ed. N. Y., Appleton-Century [1943], 351 p. [actually 385 p.].

Colyer (Sir), J. F. & Sprawson, E. C. *Dental surgery and pathology.* 8. ed. London, Longmans [1942], 1067 p.

Cowdry, E. V. *Microscopic technique in biology and medicine.* Balt., Williams, 1943, 206 p.

Eiris, E. J. *Dermatosis profesionales.* Rosario, Ruiz, 1943, 212 p.

Glaister, J. *Medical jurisprudence and toxicology.* 7. ed. Edinburgh, Livingstone, 1942, 671 p.

Ham, A. W. & Salter, M. D. *Doctor in the making; the art of being a medical student.* Phil., Lippincott [1943], 179 p.

Hewer, C. L. *Recent advances in anaesthesia and analgesia.* 4. ed. London, Churchill, 1943, 341 p.

Hooker, R. W. *Ship's doctor.* [Autobiography.] N. Y., Whittlesey [1943], 279 p.

Hoskins, M. M. & Bevelander, G. *Outline of histology.* St. Louis, Mosby, 1942, 179, 112 p.

Howles, J. K. *A synopsis of clinical syphilis.* St. Louis, Mosby, 1943, 671 p.

Hurdon, E. *Cancer of the uterus.* London, Milford, 1942, 188 p.

Kaufman, W. *The common form of niacin amide deficiency disease: aniacinamidosis.* Bridgeport, [priv. print?], 1943, 62 p.

Leonardo, R. A. *History of surgery.* N. Y., Froben, 1943, 504 p.

Loewenberg, S. A. *Medical diagnosis and symptomatology.* 6. ed. Phil., Davis, 1943, 1181 p.

Mather, K. *Statistical analysis in biology.* London, Methuen, [1943], 247 p.

Miller, S. C. [et al.]. *Textbook of periodontia.* 2. ed. Phil., Blakiston [1943], 733 p.

Moore, J. E. *The modern treatment of syphilis.* 2. ed. Springfield, Ill., Thomas, 1943, 717 p.

O'Hara, D. *Air-borne infection; some observations on its decline.* N. Y., Commonwealth Fund, 1943, 114 p.

Parsons, R. P. *Trail to light; a biography of Joseph Goldberger.* Indianapolis, Bobbs-Merrill, [1943], 353 p.

Pohl, J. F. M. & Kenny, E. *The Kenny concept of infantile paralysis and its treatment.* Minneapolis, Bruce, 1943, 366 p.

Raven, R. W. *Surgical care.* London, Arnold, [1942], 271 p.

Scoville, W. L. *The art of compounding.* 7. ed. by J. L. Powers and G. E. Crossen. Phil., Blakiston, [1943], 457 p.

Shaar, C. M. & Krouz, F. P. *Manual of fractures.* Phil., Saunders, 1943, 300 p.

Strecker, E. A. & Appel, K. E. *Discovering ourselves.* 2. ed. N. Y., Macmillan, 1943, 434 p.

Thewlis, M. W. *The care of the aged (geriatrics).* 4. ed. St. Louis, Mosby, 1942, 589 p.

Truby, A. E. *Memoir of Walter Reed; the yellow fever episode.* N. Y., Hoeber [1943], 239 p.

Truslow, W. *Body poise.* Balt., Williams, 1943, 312 p.

Urbach, E. *Allergy.* N. Y., Grune, 1943, 1073 p.

Vaughan, W. T. *Primer of allergy.* 2. ed. St. Louis, Mosby, 1943, 176 p.

Voronoff, S. *Les sources renouvelées de la vie.* [N. Y.], Brentano's, [1942], 301 p.

Yost, E. *American women of science.* Phil., Stokes, 1943, 231 p.

DEATHS OF FELLOWS

BOEHM, JOSEPH LEOPOLD, 110 East 53 Street, New York City; born in St. Louis, Missouri, May 13, 1876; died in New York City, June 29, 1943; graduated in medicine from Washington University Medical College, St. Louis, in 1899; elected a Fellow of the Academy, January 3, 1924. Dr. Boehm was a member of the State and County Medical Societies, a Fellow of the American College of Surgeons, a member of the American Urological Society, assistant urologist to Polyclinic Hospital and clinical assistant urologist to Bellevue Hospital.

FOX, ELSIE, 384 East 149 Street, New York City; born in Vienna, Austria, January 25, 1885; died in New York City, June 30, 1943; graduated in medicine from Cornell University Medical College in 1911; elected a Fellow of the Academy, October 5, 1916. Dr. Fox was a member of the State and County Medical Societies, qualified under the Workmen's Compensation Law of New York State as a specialist in roentgenology and bacteriology, and was a member of the Bronx Roentgen Ray Society.

LANDSTEINER, KARL, Rockefeller Institute, 66 Street and York Avenue, New York City; born in Vienna, Austria, June 14, 1868; died in New York City, June 26, 1943; graduated in medicine from the University of Vienna in 1891; elected a Fellow of the Academy, January 7, 1932. Dr. Landsteiner was member emeritus of the Rockefeller Institute where for seventeen years he was active in the field of research, making countless valuable contributions to medicine. He won the Nobel Prize in medicine in 1930, awarded to him in Stockholm.

VAN BEUREN, FREDERICK THEODORE, JR., 65 Fifth Avenue, New York City; born in New York City, February 10, 1876; died in Morristown, New Jersey, March 13, 1943; received the degree of A.B. from Yale University in 1898; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1902; elected a Fellow of the Academy April 7, 1910; and served the Academy as Recording Secretary from 1916 through 1919, as Vice-President from 1925 through 1927, as a member of the Committee on Admission from 1922 through 1927, and as a member of the Committee on Medical Education in 1926.

Dr. Van Beuren was associate clinical professor of surgery at the College of Physicians and Surgeons since 1929 and associate dean at that institution, 1921-34; assistant attending surgeon to Lincoln Hospital, 1910-13, Roosevelt Hospital, 1913-21; attending surgeon to Volunteer Hospital, 1915-17, Sloane Hospital for Women, 1920-38; president of the Morristown Memorial Hospital since 1933; associate visiting surgeon to the Presbyterian Hospital and consulting surgeon to the Elizabeth A. Horton Memorial Hospital at Middletown. He was a diplomate of the American Board of Surgery, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Surgical Association, and a member of the State and County Medical Societies.